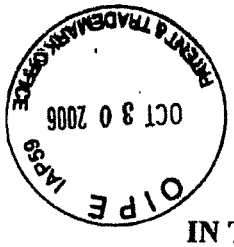
EXHIBIT 5



Re-Exam

Patent
Attorney's Docket No. 22338-10230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Control Nos.:	**90/007,542** **90/007,859**	Group Art Unit:	3991
Confirmation Nos.:	7585 ('542) 6447 ('859)	Examiner:	B.M. Celsa
Filed:	13 May 2005 ('542) 23 December 2005 ('859)		
Patent Owner:	Genentech, Inc. and City of Hope		
For:	Merged Reexaminations of U.S. Patent No. 6,331,415 (Cabilly *et al.*)		

RESPONSE UNDER 37 C.F.R. § 1.550(b)

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COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This communication responds to the non-final Office action mailed on August 16, 2006, setting an original due date of October 16, 2006. Owners timely requested an extension of time to respond. In a Decision mailed on October 17, 2006, the Office granted an extension of two weeks, to Monday, October 30, 2006, for Owners to file a response. As this reply is filed within the extended period for response, it is timely filed.

Patent Owners (Owners) respectfully request reconsideration of the claims in view of the following remarks.

REMARKS

I. Preliminary Matters

A. Information Disclosure Statement

Owners thank the Examiner for his indication that materials previously submitted to the Office have been fully considered. Owners request consideration of the additional materials provided in the accompanying information disclosure statement (PTO Form 1449).

B. Interview Summary

Owners thank Examiners Celsa, Jones and Padmashri for the courtesy of an interview held on September 27, 2006. At the interview, as summarized in the interview summary form, the representatives of Owners and the Examiners discussed a number of issues.

First, the Owners explained that the prosecution history of U.S. Patent No. 4,816,567 (the '567 patent) demonstrates that the term "or" as used in the claims has its conventional meaning (i.e., as referring to one of the enumerated alternatives). Owners explained that the actions of the PTO and of the Owners (then applicants) before and after the amendment which introduced claims 53, 57 and 63 plainly shows that neither the Owners nor the Office viewed "or" as meaning the "logical or" (i.e., meaning "and/or"). Owners indicated that they would provide the Office a summary of the relevant prosecution history of the '567 patent in this response.

Owners also sought a confirmation that "Claim Interpretation 1" and rejections premised on it were contingent on the Examiner's determination that the term "or" was being read as the "logical or" (i.e., as if the claims had been amended by replacing "or" with the words "and/or"). The Examiners concurred that this was the premise of the rejections under Claim Interpretation 1; namely, that the rejection is premised on the belief that the word "or" actually was intended to mean "and/or". The Examiners indicated that if the prosecution history and the specification showed that the term "or" was used with its ordinary meaning (i.e., as referring to alternatives), the rejections premised on Claim Interpretation 1 would be withdrawn.

Owners also discussed the relationship between the claims of the '415 and '567 patents. In particular, Owners referred to the explanation in their Response of November 25, 2005, which explained why the claims of the '415 patent cannot be interpreted as defining a "genus" of methods that includes "species" methods defined in the '567 patent. The Examiners confirmed

that rejections in the First Office Action based on such a finding were withdrawn in favor of the new rejections under the two claim interpretation theories set forth in the Office action mailed August 16, 2006 ("Second Office Action.")

Second, Owners discussed the obviousness-type double patenting rejections based on "Claim Interpretation 2." Owners emphasized the importance of using the proper perspective when considering the teachings of the various references cited in the Office Action; namely, what the references would have taught or suggested to a person of ordinary skill in the art in early April of 1983. Owners explained that each of the experts who had previously submitted declarations under 37 C.F.R. § 1.132 was qualified to explain this perspective based on their respective experiences in the relevant time frame. Owners further addressed the teachings of the various cited prior art references, and explained why the '567 patent claims, considered in view of any or all of these references, would not have rendered the claims of the '415 patent obvious.

The Examiners agreed that the obviousness-type double patenting questions are to be evaluated by considering the question of non-obviousness of the '415 claims in view of the '567 patent claims, taken in view of other prior art. The Examiners also agreed that the question of "obviousness" must be considered from the perspective of a person of ordinary skill in the art in early April of 1983, including what the references would have taught such a person at that time.

Owners requested that the Examiners review the prosecution histories of the '415 and '567 patents. Owners noted, for example, that the Office had previously considered most of the references now being employed in the obviousness-type double patenting rejections. The Examiners indicated they would consider the prosecution histories of the '415 and '567 patents incidental to the consideration of Owners' response.

Third, Owners discussed the complex physical structure of immunoglobulins and the limited understanding that persons of ordinary skill in the art had in early April of 1983 regarding the processes of immunoglobulin gene expression and subsequent production and assembly of immunoglobulin proteins. The Owners also discussed the experiences of those working in the art in the relevant time frame concerning production of monomeric eukaryotic proteins having molecular weights much lower than those of tetrameric immunoglobulins. The

Examiners indicated they would consider information and evidence provided by Owners related to these issues.

Fourth, Owners expressed their opinion that a declaration provided by a third party (Dr. Baltimore) was not a patent or printed publication, and as such, could not serve as a basis for finding of a substantial new question of patentability, and could not be considered during an ex parte reexamination proceeding. Owners also referred to the opinions of Dr. Douglas A Rice provided with the first response concerning the Rice publication.

Finally, Owners sought and received a confirmation that information previously provided in an Information Disclosure Statement (IDS) had been fully considered, and that no further information regarding the submitted information was needed by the Office. Owners also apprised the Examiners of the status of litigation involving the '415 patent–specifically, that MedImmune v. Genentech, 427 F.3d 958, 76 U.S.P.Q.2d 1914 (Fed. Cir. 2005), had been scheduled for argument before the Supreme Court of the United States on October 4, 2006. As indicated at the interview, Owners provide for the convenience of the Office copies of the merits briefs filed by the parties in that proceeding in the concurrently filed IDS.

Owners now inform the Office that argument before the Supreme Court did occur on October 4, 2006 and are providing for convenience of the Office a copy of the transcript of that argument (downloaded from the Supreme Court website) in the accompanying IDS.

C. Observation on the Office's Determination Concerning Cumulative Prior Art

Owners observe that the Office has found the teachings of 1982 Valle to be cumulative to the teachings of Deacon, and the teachings of Oi to be cumulative of the teachings of Ochi. Owners reserve their right to contest the finality of any further Office Action on the basis of information contained exclusively in either 1982 Valle or Oi in view of these findings and the reliance by the Office on Deacon and Ochi.

D. Past PTO Actions Support Finding the '415 Claims Separately Patentable Over the '567 Claims

Owners invite the Office to review the summary of the prosecution events of the '415 and '567 patents provided in Owner's First Response, dated November 25, 2005 (First Response). See First Response, pages 8 to 15; Declaration of Wendy Lee. Owners submit that the past

record of actions by the Office in connection with the '415 and '567 patents shows a consistent pattern of findings by the Office that claims in the form of the '415 patent claims are separately patentable over the claims in the form of the '567 patent claims, alone or in view of the cited references.

Indeed, the question of patentability of claims in the form of the '415 patent claims over claims in the form of the '567 patent claims was considered directly by the Office several times.

- The Office issued separate patents with claims corresponding to the '567 and '415 claims, respectively, to different parties on the same day. Specifically, on March 29, 1989, the Office issued the '567 patent to Cabilly et al., and U.S. Patent No. 4,816,397 to Boss et al.

- The Office did not involve the '567 patent claims (as well as other claims that did not require heavy and light chains to be produced in one host cell) in the interference proceedings based on claims in the form of the '415 patent claims (i.e., Interference No. 102,572). See First Response, pages 10-12; Lee Declaration, Exhibits L; M, and N; application serial no. 07/205,419 (i.e., the application that matured to the '415 patent), paper no. 18.

- During the prosecution of the '415 patent, the Office imposed a restriction requirement differentiating claims to embodiments requiring heavy and light immunoglobulin chains from embodiments requiring only one or the other chain. See '419 application, paper 11; Lee Declaration, Exhibit I.

- In an interview following termination of the interference proceeding held on October 4, 2001, the Office indicated that there were no obviousness-type double patenting issues raised by the 415 claims relative to the '567 patent claims. See '419 application, paper no. 19; Lee Declaration, ¶¶ 20-23.

As Owners explained during the interview on September 27, 2006, these past findings of the Office reflect a consistent view that the '415 patent claims are separately patentable over, and in particular, are neither anticipated by nor obvious over the '567 patent claims. These past findings are probative of the past opinions of the Office as to the non-obviousness of the '415 patent claims relative to the '567 patent claims.

Owners note that, at page 32 of the Second Office action, the Office dismisses this record of past determinations by the Office by asserting that the substantial new questions of patentability being addressed in the present reexamination are based on newly cited references and "a combined teaching with the '567 claims neither of which was considered by the

Examiner" in the earlier proceedings. First, Owners note that the Office is not relying upon prior art to support the rejections of the independent and certain dependent claims of the '415 patent under its "Claim Interpretation 1" theory of the '567 patent claims. Second, Owners note that almost all of the references the Office now relies on, as well as various other references that provide teachings comparable to those in the subsidiary references the Office now cites, were before the Office during the prosecution of the '415 patent. For example, Rice, Oi, Ochi, Kaplan, Accolla, Deacon, and Valle 1981 were all cited to the Office during the prosecution of the patent.

Furthermore, publications describing the co-transformation methodology of Axel (e.g., Wigler et al., Cell 16: 777-85 (1979), which includes the inventors of Axel as co-authors) and the protein-folding methodology of Builder (e.g., US 4,512,922 to Jones et al.) were made of record in the application that matured to the '415 patent. Dallas, as Owners discuss below, is of marginal relevance. Thus, Owners submit that the Office has in fact previously considered all of the relevant technical teachings of the references now cited to support the double patenting rejection, or evidence that is cumulative to those references, with respect to the patentability of the claims of the '415 patent over the '567 claims.

II. Response to Rejections

A. Summary of the Rejections

In the Second Office Action, the Office rejects all of the claims of U.S. Patent No. 6,331,415 for reasons of "obviousness-type" double patenting over the claims of U.S. Patent No. 4,816,567. In doing so, the Office articulates two distinct constructions of the '567 patent claims.

First, the Office advances a theory that the claims of the '567 patent, through use of the term "or," actually recite three distinct methods. Two of these three methods – the two that do not correspond to the actual claim language – are asserted to anticipate, and thus render unpatentable, claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 patent. This rejection depends on the Office's determination that the term "or" as used in the claims actually means "and/or."

Second, the Office sets forth an alternative claim interpretation that employs the conventional (and correct) meaning of the claim term "or" – namely, that it refers to alternatives. The Office nonetheless imposes rejections based on a finding that the claims of the '415 patent are "obvious" over the claims of the '567 patent, either considered alone or in conjunction with a variety of references. At page 22, the Office rejects claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 patent over the claims of the '567 patent, taken in view of Axel, Rice or Kaplan, further in view of Dallas, and further in view of Deacon, Valle 1981 or Ochi.

Third, at pages 26-35 of the Office Action, the Office rejects the remaining dependent claims of the '415 patent (i.e., claims 5-10, 12, 14, 19-20, 22, 26-32 and 34-36). The basis of the rejection is set forth as (i) the finding that claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 patent are unpatentable under either "Claim Interpretation 1" or "Claim Interpretation 2," and (ii) each dependent claim is obvious when taken further in view of the identified prior art.

Owners respectfully traverse the rejections set forth in the Office Action.

B. The Rejection of Claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 Patent Based on "Claim Interpretation 1" Has No Basis in Law or from the File Wrapper of the '567 Patent

At pages 6 to 21 of the Second Office Action, the Office sets forth the first of its two theories for interpreting the claims of the '567 patent (labeled "Claim Interpretation 1"). Under this rationale, the claim term "or", as used in the '567 patent claims, refers not to alternatives (the conventional meaning of "or") but to what the Office labels the "logical or" (i.e., that it means "and/or"). With that interpretation, the Office concludes that the '567 patent claims "encompass" three distinct methods:

a. light chain- and heavy chain -encoding DNA is inserted into 2 separate vectors for individual expression in 2 different hosts ("or" embodiment);

b. light chain- and heavy chain -encoding DNA is inserted into 2 separate vectors for coexpression of both vectors in 1 host ("and" embodiment); and

c. light chain- and heavy chain -encoding DNA is inserted into 1 vector for expression in 1 host ("and" embodiment).

The Office then asserts that claims 1-2 and 5-7 of the '567 patent, interpreted in this manner, "read on" (and thus anticipate) claims 1, 13, 15-18, 21 and 33 of the '415 patent. Relying on this rationale, the Office rejects claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 solely on the basis of claims 1-2 and 5-7 of the '567 patent. Owners request reconsideration of this ground of rejection.

1. The Owners Did Not Expressly Redefine the Meaning of the Claim Term "or" as Used in the '567 Claims

In its ordinary meaning, "or" is understood as stating alternatives. Kustom Signals, Inc. v. Applied Concepts, Inc., 264 F.3d 1326, 1331, 60 U.S.P.Q.2d 1135, 1138 (Fed. Cir. 2001); Schumer v. Lab. Comp. Sys. Inc., 308 F.3d 1304, 1311, 64 U.S.P.Q.2d 1832, 1838 (Fed. Cir. 2002) ("We have consistently interpreted the word "or" to mean that the items in the sequence are alternatives to each other"); Brown v. 3M, 265 F.3d 1349, 1352, 60 U.S.P.Q.2d 1375, 1377 (Fed. Cir. 2001) (interpretation of "or" involved a "plain reading of the claim text"). In fact, the Office readily admits as much at page 10 of the Second Office Action: "normally ... 'or' is interpreted to mean that the items in a sequence recited in a claim are alternatives to each other."

As noted in the M.P.E.P., "the words of the claim must be given their plain meaning unless applicant has provided a clear definition [to the contrary] in the specification." M.P.E.P. § 2111.01[I] (emphasis added), citing In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); see also Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004) (noting that "ordinary, simple English words whose meaning is clear and unquestionable" absent any indication that their use in a particular context changes their meaning, "are construed to mean exactly what they say"). Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." M.P.E.P. § 2111.01.III (emphasis added), citing Multiform Desiccants Inc. v. Medzam Ltd., 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998); see also Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999); M.P.E.P. § 2173.05(a).

No special definition has been set forth for the claim term "or" in the '567 patent specification, and as explained below, the prosecution history, considered properly, does not suggest that Owners redefined the term.

2. The Prosecution History of the '567 Patent Shows that "or" as Used in the '567 Patent Claims Has Its Ordinary Meaning

The prosecution history of application Serial No. 06/483,457 (the application that matured to the '567 patent) plainly demonstrates that Owners used the claim term "or" in a conventional manner to refer to alternatives – not, as the Office suggests, as meaning "and/or" (the "logical or").

As originally filed, the '567 patent application contained claims 1 through 52. Five of these claims were independent method claims. One of them, Claim 51, was directed to a "method for preparing heavy chain or light chain."[1] Claims 42, 47 and 49, on the other hand, were directed to processes requiring both heavy and light chains to be produced in the same cell.[2] The original claims plainly show that Owners employed the term "or" when alternatives were intended, and the term "and" when conjunctive relationships were intended.

In the Office Action mailed on April 26, 1985, the Office rejected all of the original claims (i.e., claims 1-52). In a response filed on October 28, 1985, Owners canceled all of the pending claims and presented new claims 53-88. The new set of claims contained several independent method claims, including claims 53, 68 and 78. The first step of each of these new independent claims was directed to preparing a DNA sequence. The options for the prepared DNA, as specified in these claims, were as follows:

> Claim 53 recited "preparing a DNA sequence encoding an immunoglobulin heavy or light chain, or an immunoglobulin Fab region, of known specificity."[3]
>
> Claim 68 recited "preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain of known specificity wherein the constant regions are homologous to the corresponding regions of an antibody of a first mammalian species and the variable regions thereof are

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1 See '567 prosecution history, page 60 of original claims and specification.

2 See '567 prosecution history, pages 57-60 of original specification.

3 See '567 prosecution history, April 26, 1985 response at page 2. As with original claim 51, claim 53 recited that the transformation of the host cell was with "an immunoglobulin heavy or light chain," as well as reciting that the transformation could alternatively be with "an immunoglobulin Fab region" and that "heavy chain, light chain or Fab" is recovered from the host cell culture.

> homologous to the variable regions of an antibody derived from a second, different mammalian species."[4]
>
> Claim 78 recited "preparing a DNA sequence encoding an altered immunoglobulin heavy or light chain of known specificity wherein the amino acid sequence of the immunoglobulin has been varied in predetermined fashion from that of mammalian antibody."

Claims 57, 63 and 65 depended from claim 53 and claimed a result that required production of both the heavy and the light immunoglobulin chains.[5] By contrast, no claims dependent from claims 68 or 78 required production of heavy and light chains. Claim 68 ultimately issued in slightly modified form as claim 1 of the '567 patent.

In the next Office action, dated February 26, 1986, the Examiner rejected claims 57 and 63 under 35 U.S.C. § 112, second paragraph, as being improperly dependent on then-pending claim 53. In particular, the Examiner stated:

> Claims 57 and 63 are improper dependent claims in that they indicate that both heavy and light chains are contained in a vector and that they are produced together. Claim 53 from which claims 57 and 63 depend is a method to clone a light chain, a heavy chain or a Fab region, not two chains together. (emphasis added).

In other words, the Examiner plainly and immediately recognized that independent claim 53, which employed the term "or," was inconsistent on its face with the requirements specified by dependent claims 57 and 63, which required a conjunctive relationship between the alternatives recited in independent claim 53 (i.e., light chain or heavy chain or Fab fragment).

In response to this rejection, Owners attempted to fix the perceived problem by amending "or" in claim 53 to read "and/or." Owners explained:

> Claims 53 -88 were rejected under 35 U.S.C. 112(b) [sic] as being indefinite for various recitations. The amendments to the claims render moot certain elements of this rejection. ...

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[4] See '567 prosecution history, October 28, 1985 response at page 3-4.

[5] Added claim 63, which depended from claim 53, recited that heavy and light chain are recovered from the host cell culture that has been transformed and are reconstituted to form an immunoglobulin. Dependent claims 57 and 65, also dependent from claim 53, required both heavy chain - and light chain - encoding DNA. Claim 57 recited that heavy chain and light chain were both contained in the vector used to transform the host cell, and claim 65 recited that the heavy and light chain are to be coexpressed in the same host cell.

> Claims 57 and 63 were said to be improper dependent claims in indicating that both heavy and light chains are produced together, claim 53 being said to exclude such a possibility. Claim 53 has been amended to clearly point out that the chains are produced together or separately.

'567 prosecution history, Amendment filed July 28, 1986, page 18 (emphasis added). Thus, in response to the § 112, second paragraph rejection, Owners sought to change the term "or" to explicitly read "and/or" to define a "logical or" relationship between the options listed in claim 53, consistent with the requirements of dependent claims 57 and 63. The record thus plainly shows that the Owners accepted the Examiner's understanding that the term "or" was being used with its conventional meaning (i.e., that it was being used in claim 53 to refer to alternatives, and did not have a "logical or" meaning). In other words, rather than asserting that the term "or" actually meant "and/or," Owners sought to expressly replace the term "or" with the words "and/or."

By contrast, Owners did not seek to amend the "or" clause in claim 68. Unlike claim 53, there were no claims dependent from claim 68 requiring heavy- and light chain -encoding DNA, or requiring heavy and light chains to be produced in the same transformed host cell. Critically, there was no rejection of claim 68 under § 112, second paragraph, comparable to the rejection of claim 53. The distinct treatment of claim 53 relative to claim 68 reinforces the fact that the Owners and the Examiner both viewed the term "or" as having precisely the same meaning (i.e., its conventional alternative meaning).

The subsequent events in the prosecution history do not alter this unequivocal record. After reviewing the amendment to claim 53, the Office, in an Action dated November 26, 1986, imposed a new rejection of amended claim 53 under §112, second paragraph. The stated reason for the rejection was that the amended claim was "unduly alternative in the recitation of 'and/or' in step (b) and (d)." The Examiner noted that "Applicants may wish to utilize Markush language to set forth the various combinations of sequences." The Examiner also indicated that she would maintain the rejection regarding the improper dependency of claims 57 and 63 until the "and/or" language was corrected. In subsequent responses,[6] Owners twice sought to amend claim 53 to

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[6] In the May 29, 1987 amendment under 37 C.F.R. §1.136(a), Owners changed the phrase "and/or" to "selected from the group of an immunoglobulin heavy chain or light chain or Fab region." After the Examiner indicated that the Markush language required the use of the term "and" rather than "or" on May 19, 1988, Owners

comply with the Examiner's Markush suggestions. Finally, in response to an Advisory Action,[7] Owners canceled the claims in question (53, 57 and 63), indicating that these claims "[would] be resubmitted in a continuing application based on this application."[8]

Claims 68, 70, 71, 73, 74, 76, and 77, the only claims remaining in the '457 application at that point, were allowed and issued as claims 1-7 of the '567 patent. All seven of the claims employ the unambiguous phrase "heavy chain or light chain." Notably, not once was the "or" language in claim 68 amended. Similarly, there was no rejection of claim 68 suggesting that the term "or" was being used in an improper or indefinite manner. Thus, there is nothing in the prosecution history to suggest that the term "or," as used in claim 68, was intended or understood to have any meaning other than its ordinary meaning (i.e., referring to alternatives). Moreover, nothing from the rejections regarding the form of claims 53, 57, and 63 was or could be imputed by the Examiner to apply to claim 68, which did not have dependent claims analogous to claims 57 and 63.

Thus, the prosecution history of the '567 patent, considered accurately and in proper context, plainly demonstrates that the Owners did not "redefine" the term "or" as used in granted claim 1 to have a meaning other than its ordinary meaning (i.e., referring to alternatives). It also demonstrates that the Examiner handling the application did not interpret the term "or" to mean "and/or." The record plainly does not support the interpretation of the file wrapper suggested in the Office Action.

3. The Specification of the '567 Patent Does Not Expressly or Implicitly "Redefine" the Claim Term "or"

The Office portrays Owners' identification of support in the specification for the new claims added by the October 28, 1985 amendment as an indication that Owners redefined the claim term "or" as used in claim 53. Specifically, the Office asserts that because the passages

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amended claim 53 from "or light chain, or" to ", light chain, and" in the May 11, 1988 Response under 37 C.F.R. §1.116.

[7] In the May 19, 1988 Advisory Action, the Examiner noted among other things that "consisting" was needed after the term "group" in claim 53 to correctly recite a Markush grouping.

[8] Claim 78 and its dependent claims (78, 81, 84, and 87-90) were cancelled by the May 11, 1988 Response filed with the Notice of Appeal on May 11, 1988.

referred to by the Owners describe both "or" and "and" embodiments, the Owners must have intended to redefine the term "or" as it is used in the claims of the '567 patent.

There is no basis for the Office's assertions. The identified passages of the specification do, in fact, support various embodiments of the inventions defined by the '567 and '415 patent claims, as well as then-pending claim 53. However, the mere identification of various sections of the specification providing support for a claim cannot be portrayed as an attempt to redefine the meaning of the claim term "or" as the Office asserts. The section of the October 28, 1985, response tabulating pages in the specification where support may be found certainly is not a form of expression that suggests an intent to redefine terms having ordinary and well-accepted meanings, such as the word "or."

Similarly, there is nothing in the cited passages of the specification that refers to the term "or" or how it should be interpreted. These passages are simply describing different embodiments of inventions that were later claimed in different patents. The language used in these sections simply differentiates various approaches toward transformation of host cells, production of various types of vectors, and production of immunoglobulin chains or immunoglobulin molecules. These passages do not represent an effort by the Owners to redefine the term "or" as the Office suggests.

4. The Office Does Not Accurately Identify the Differences Between the '415 and '567 Claims

At page 16 of the Second Office Action, the Office describes what it believes are the differences between the '567 patent and the '415 patent:

> The Cabilly 1 reference [i.e., the '567 patent] patented invention *differs* from the instant patent [i.e., the '415 patent] since:
>
> a. reference Cabilly 1 produces a (replicable expression) vector comprising DNA encoding immunoglobulin heavy or light chain for transforming and culturing of a host cell; whereas the instant patent requires that the vector comprise DNA encoding immunoglobulin heavy and light chain for transforming and culturing of a single host cell, and
>
> b. reference Cabilly 1 is directed to the production of chimeric immunoglobulins (i.e. a species); whereas the instant invention produces an immunoglobulin (i.e. is generic).

The Office's analysis of the differences between the '567 and '415 patent claims is incorrect in two significant respects.

First, the Office asserts that the '567 (Cabilly 1) claims are "directed to production of chimeric immunoglobulins." The '567 claims are not. The '567 claims require only that the claimed process result in a recovered chimeric immunoglobulin light chain, or a recovered chimeric immunoglobulin heavy chain (see, e.g., final step (e) of the '567 claim 1). There is no requirement in the '567 claims that the recovered chimeric heavy or recovered chimeric light immunoglobulin chain be incorporated into an assembled immunoglobulin molecule or an immunologically active immunoglobulin fragment, as required by the '415 patent claims.[9]

Second, it overlooks several of the most important distinctions between the two sets of patent claims. Specifically, the Office focuses only the fact that the '567 claims "produce[ ] a (replicable expression) vector comprising DNA encoding immunoglobulin heavy or light chain for transforming and culturing of a host cell," while the '415 claims "require[ ] that the vector comprise DNA encoding immunoglobulin heavy and light chain for transforming and culturing of a single host cell."[10] This overly narrow focus ignores other significant distinctions between the claims.

For the convenience of the Examiner, Owners provide Exhibit A, which compares, in table format, claim 1 of the '415 patent to claim 1 of the '567 patent. Owners also refer the Office to the tables provided in the Owners First Response.[11]

Exhibit A illustrates three significant distinctions between the two sets of patent claims.

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[9] The Office correctly observes that the nature of the immunoglobulin chains implicated by the '415 and '567 patent claims differs. Specifically, it correctly observes that the heavy or light chain polypeptides that result from the '567 claims are "chimeric" in nature, while there is no such requirement of the heavy or light immunoglobulin chains being produced incidental to the method of the '415 patent claims.

[10] Owners also note that the Office incorrectly characterizes the '415 claims as appearing to require that the two DNA sequences be contained in a single vector. This is not consistent with the claims of the '415 patent (see, e.g., claims 2 and 3 of the '415 patent, which further limits claim 1 of the '415 patent by specifying that the two sequences are one either one or two vectors).

[11] See First Response, Table 1 and Exhibit E. The comparisons provided in the first response were done primarily to illustrate comparable claim elements in the two sets of claims for purposes of the species-genus analysis discussed in the First Office Action and the First Response.

- First, the '415 claims require the host cell to be transformed with two DNA sequences, a first DNA sequence encoding at least a variable domain of a light immunoglobulin chain, and a second DNA sequence encoding at least the variable domain of a heavy immunoglobulin chain. The '567 claims do not require that a single host cell be transformed with two DNA sequences (see, e.g., step (a), "preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain").

- Second, the '415 claims require that the heavy and light chain polypeptides "be produced as separate molecules in said transformed single host cell" (see step (ii) of claim 1). Because there is no requirement in the '567 claims for production of more than one immunoglobulin polypeptide, there is no mention, much less a requirement for, production of the heavy and light chain polypeptides as separate molecules in the '567 patent claims.[12]

- Third, the '415 claims require the assembly of the heavy and light chain polypeptides that have been independently produced in the cell into an immunoglobulin molecule or an immunologically functional immunoglobulin fragment (see lines 1-5, and step (ii) of claim 1). There is no requirement in the '567 claims that the individual recovered chimeric heavy chain, or recovered light chain in final step (e) be assembled into an immunoglobulin molecule or fragment.

Each of these distinctions would have been appreciated by a person of ordinary skill in the art in early April of 1983 as being significant, as will be more fully explained in section II.C, below, in connection with the rejections based on Claim Interpretation 2. Because the Office fails to appreciate and address each of the distinctions between the claims of the two patents, the rejections of the claims of the '415 patent under either of the two claim interpretations advanced for the '567 claims are improper.

5. The '567 Claims Do Not "Read On" and Thus Render Unpatentable the '415 Patent Claims for Reasons of Obviousness-Type Double Patenting

Settled law on "obviousness-type" non-statutory double-patenting recognizes two types of relationships between claims that support finding a later issuing claim unpatentable. The first is where an invention defined by the claims of a first-issuing patent renders an invention defined by a later-presented claim obvious in view of prior art. In that situation, the burden on the Office

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[12] As the Office has done, Owners have used claim 1 of the '415 patent and claim 1 of the '567 patent for an illustrative comparison of the claims of the two patents. Distinctions exist between these claims and other independent and dependent claims in the two patents, which Owners have previously discussed. See, e.g., First Response, Table 1 and Exhibit E; see also, section II.C, infra.

is to demonstrate that the differences between the two sets of claims would have been obvious, within the meaning of 35 U.S.C. § 103, in view of the prior art. See M.P.E.P. § 804; In re Longi, 759 F.2d 887, 892, 225 U.S.P.Q. 645, 652 (Fed. Cir. 1985) ("double patenting of the obviousness type ... is 'analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. § 103,' except that the patent principally underlying the double patenting rejection is not considered prior art").

A less common situation arises when the claims of the first-issuing patent define a species and the later presented claims define a genus which wholly encompasses that species. In that situation, courts have employed a simplified analysis: the earlier-claimed "species," by operation of law, anticipates the later-presented "genus" claim. Since anticipation is the "epitome of obviousness,"[13] courts have held the later-presented claims unpatentable due to reasons of "obviousness-type" double-patenting. In re Berg, 140 F.3d 1428, 46 U.S.P.Q.2d 1226 (Fed. Cir. 1998), In re Emert, 124 F.3d 1458, 1462, 44 U.S.P.Q.2d 1149, 1153 (Fed. Cir. 1997); In re May, 574 F.2d 1082, 197 U.S.P.Q. 601 (C.C.P.A. 1978). The operative legal analysis in this second situation, however, is based on the law of anticipation of a "genus" by an earlier disclosed (claimed) "species" within that "genus."

The rejections of claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 patent based on "Claim Interpretation 1" for the claims of the reference '567 patent, are not presented using the Graham v. John Deere framework required to establish "obviousness." Specifically, the Office has not set forth a prima facie showing as to why the three significant distinctions between the '415 and '567 patent claims noted above would have been obvious to a person of ordinary skill in the art in early April of 1983.

Instead, the Office has rejected the '415 patent claims on the grounds that those claims define a genus that is anticipated by species defined in the earlier-issued '567 patent claims. The

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[13] "Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim. Soundscriber Corp. v. U.S., 360 F.2d 954, 960, 148 U.S.P.Q. 298, 301 (Ct.Cl.1966). A prior art disclosure that 'almost' meets that standard may render the claim invalid under § 103; it does not 'anticipate.' Though it is never necessary to so hold, a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness,' In re Fracalossi, 681 F.2d 792, 215 U.S.P.Q. 569 (C.C.P.A. 1982). The reverse is not true, for the need to determine obviousness presumes anticipation is lacking." Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548, 220 U.S.P.Q. 193, 199 (Fed. Cir. 1983).

finding of such a genus-species relationship, however, is premised on the two errors in claim interpretion explained above, each of which makes the "Claim Interpretation 1" rejection of the '415 patent claims improper.

First, the Office mistakenly interprets the claim term "or" to mean "and/or," and upon this basis, incorrectly construes the '567 claims as "reading on" or "encompassing specification embodiments where:

a. light chain- and heavy chain -encoding DNA is inserted into 2 separate vectors for individual expression in 2 different hosts ('or' embodiment);

b. light chain- and heavy chain -encoding DNA is inserted into 2 separate vectors for coexpression of both vectors in 1 host ('and' embodiment); and

c. light chain- and heavy chain -encoding DNA is inserted into 1 vector for expression in 1 host ('and' embodiment)."

See Second Office Action, paragraph bridging pages 19-20.

Second, the Office employs an inaccurate and incomplete assessment of the differences between the claims of the '415 and '567 patents. Specifically, at page 19 of the Second Office Action, the Office incorrectly finds that claims 1, 21, and 33 (the independent process claims of the '415 patent) "are drawn to methods for producing a genus of immunoglobulins; while Cabilly ['567] claim 1 is directed to methods for producing "chimeric" immunoglobulin chains, which is a species of the instant immunoglobulin genus." The Office similarly finds that this "species-genus" relationship exists between claims 5 and 7 of the '567 patent, and claims 15-16 (vector) and 17-18 (host cell) of the '415 patent. The Office relies on this relationship to find claims 2, 3, 11 and 25 "obvious" over claims 1-2 and 5-7 of the '567 patent.

The Office's determination that the '567 claims anticipate the '415 claims as species-genus is dependent on its incorrect interpretation of the term "or" as used in the '567 claims as meaning "and/or." Such an interpretation is plainly inconsistent with the clear record of examination of the '567 patent on this point, as explained above. Owners respectfully submit that the Office's reasoning and the corresponding rejection of the '415 patent claims is factually incorrect and legally unsupportable, and should be withdrawn.

Indeed, no reasonable intepretation of the claims of the '567 or '415 patents can support a conclusion that the '567 claims anticipate the '415 claims as species-genus. As explained in the Owners' First Response, the methods defined by each of the '415 claims require features and elements that are not required by or recited in the '567 patent claims. See, e.g., table at pages 24-25 of Owner's First Response, comparing claim 1 of the '415 patent to claim 1 of the '567 patent. For example, the '567 claims do not require the production in a single host cell of both heavy and light immunoglobulin chains. The '567 claims also do not require the method to result in an immunoglobulin molecule or an immunologically active fragment, as is required by all of the '415 patent claims. As a consequence, one practicing the process of the '567 patent claims does not by necessity infringe the '415 patent claims. Thus, because the '567 patent claims do not define "species" of methods fully within the scope of the methods defined in the '415 patent claims, the '567 patent claims, properly construed, do not "anticipate" the '415 patent claims, and render them unpatentable for reasons of "obviousness-type" double patenting.[14]

Moreover, as Owners explained in their November 25, 2005, response (see, e.g., pages 26-27), the fact that the '567 claims and the '415 claims might "read on" common subject matter is irrelevant to an obviousness-type double patenting analysis. Case law makes absolutely clear that "domination" of common subject matter by claims in two different patents is irrelevant to an obviousness-type double patenting inquiry. See In re Kaplan, 789 F.2d 1574, 1578, 229 U.S.P.Q. 678, 682 (Fed. Cir. 1986) ("Domination is an irrelevant fact"); In re Sarett, 327 F.2d 1005, 1014, 140 U.S.P.Q. 474, 482 (C.C.P.A. 1964) ("it is elementary that readability of a claim on the subject matter of another claim (domination) is neither determinative of the double patenting issue nor demonstrative that claims are directed to the same invention"). The proper inquiry, as articulated by relevant case law and restated in the M.P.E.P., involves a comparison of what the claims of the '415 patent require compared to what the claims of the '567 patent require.

Accordingly, Owners respectfully request that the Office withdraw rejections based on "Claim Interpretation 1" of the '567 patent claims.

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[14] In these respects, the Office is invited to review the detailed comparison between the claims of the '415 patent and the claims of the '567 patent provided at pages 24 to 32 of Owner's First Response.

6. The Office May Not Use the Disclosure of the '415 and '567 Patents to Supply Missing Elements of the '415 Claims Relative to the '567 Claims

(a) Settled Law Holds that the Office May Not Use Owners' Own Disclosure in an Obviousness-Type Double Patenting Rejection to the Missing Elements of the Later Claim

It is legally improper for the Office to use the specification of the '567 patent to read into the '567 patent claims unclaimed features or elements that are required by the claims of the '415 patent. Moreover, the Office may not use the "teachings" of the patent specification or claims to find motivation, guidance or support for modifying the '567 patent claims.

Settled law holds that, when comparing the claims for obviousness-type double patenting purposes, "the [earlier] patent disclosure may not be used as prior art." In re Vogel, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 622 (C.C.P.A. 1970) (emphasis added); see also General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1281, 23 U.S.P.Q.2d 1839, 1846 (Fed. Cir. 1992) ("Our precedent makes clear that the disclosure of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, even where the disclosure is found in the claims." (emphasis in original; citations omitted); In re Kaplan, 789 F.2d 1574, 1579, 229 U.S.P.Q. 678, 682 (Fed. Cir. 1986) ("the patent disclosure may not be used as prior art"); Chisum, Patents, §9.03 [1][a] (2005).

A patent specification may be employed to interpret the meaning of an unclear claim term or element. However, if the meaning of the claim term or element is clear, there is no need to resort to the specification for this "definitional" purpose. And certainly, the Office cannot, under the guise of a "definitional" purpose, use the specification to supply elements or features found in the specification that are not present in the claims of the reference patent.

In the present case, the '415 claim elements of (i) producing heavy and light immunoglobulin chain polypeptides as separate molecules in a single host cell, and (ii) forming an immunoglobulin molecule or immunologically functional fragment, are not present in the '567 patent claims. The use by the Office of the '567 patent specification to add these elements to the '567 patent claims is plainly improper.

(b) The Antigen Binding Language in the '567 Patent Claims Refers to the Structure of the Variable Domain of the Claimed Immunoglobulin Heavy or Light Chains, and Does Not Require Assembly of the Chains into a Functional Immunoglobulin Molecule or Fragment

The Office asserts that the phrase "having specificity for a particular known antigen" in the '567 patent claims would have been understood by a person of ordinary skill in the art as requiring or suggesting assembly of the recovered chimeric light or heavy immunoglobulin chain of the '567 claims into a functional antigen-binding immunoglobulin. The interpretation advanced by the Office is incorrect.

The '567 patent is directed to methods of producing novel immunoglobulin chains which are "chimeric." The specification explains that:

> Typically, in these chimeric antibodies, the variable region of both the light and heavy chains mimics the variable regions of antibodies derived from one species of mammals, while the the constant portions are homologous to the sequences in antibodies derived from another. One clear advantage to such chimeric forms is that, for example, the variable regions can conveniently be derived from presently known sources using readily available hybridomas or B cells from non human host organisms in combination with constant regions derived from, for example, human cell preparations. While the variable region has the advantage of ease of preparation, and the specificity is not affected by its source, the constant region being human, is less likely to elicit an immune response from a human subject when the antibodies are injected than would the constant region from a non-human source.

See Column 6, line 54 to Column 7, line 2 (emphasis added). In the context of an individual chimeric heavy chains or chimeric light chains, the '567 patent uses "specificity" to describe the amino acid residues within the variable domain of a heavy (or light) chain that confer specificity.

Similarly, at column 3, lines 43-61, the specification provides:

> The amino acid sequence runs from the N-terminal end at the top of the Y to the C-terminal end at the bottom of each chain. At the N-terminal end is a variable region which is specific for the antigen which elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody....

> The remaining portions of the chain are referred to as constant regions and within a particular class do not to [*sic*] vary with the specificity of the antibody (i.e. the antigen eliciting it). (emphasis added)

Thus, in the context of an individual chimeric heavy chain or individual chimeric light chain, the '567 patent specification employs the term "specificity" to refer to the amino acid residues within the variable domain of a heavy (or light) chain that confer specificity.

Owners also provided a declaration submitted by Dr. Timothy Harris under 37 C.F.R. § 1.132 with the Owners' First Response. In his First Declaration, Dr. Harris explains why the Office's reading of the phrase is not consistent with how a person of ordinary skill in the art would have read the phrase in early April of 1983.[15] As Dr. Harris explained in his First Declaration, a person of ordinary skill in the art at that time would:

> ...view that phrase as it is used in the claims of the '567 patent as referring to amino acid sequences within the variable domain of the individual chimeric heavy chain or light chain polypeptide that confer antigen binding specificity. In such a chimeric polypeptide, these sequences would be derived from the variable domains of an antibody or an antibody fragment exhibiting an antigen binding function.

Second Harris Declaration, ¶ 13. As explained above, the specification of the '567 patent consistently supports, rather than contradicts, Dr. Harris's interpretation of this phrase.

Despite this clear record, the Office takes the position that references to antigen-binding in the '567 patent claims necessarily mean that individual recovered light or heavy chain polypeptides pursuant to the '567 claims are to be assembled into "functional" immunoglobulin molecules or fragments required only by the '415 claims. The Office bases its assertions on two theories.

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[15] See M.P.E.P. § 716.01 et seq. (declarations submitted to traverse a rejection are entitled to consideration and when declaratory evidence is determined to be unpersuasive, the Office must "specifically explain" its determination; "[g]eneral statements such as 'the declaration lacks technical validity' or 'the evidence is not commensurate with the scope of the claims' without an explanation supporting such findings are insufficient."); In re Zeidler, 215 U.S.P.Q. 490 (C.C.P.A. 1982) (Board of Appeals may not substitute its judgment for that of an established expert in the art); In re Oelrich, 198 U.S.P.Q. 210, 214-15 (C.C.P.A. 1978) ("To the extent that all of the affidavits express opinions, they are the opinions of men conceded to be of ordinary skill in the art based on information uniquely within their competence bearing on the level of ordinary skill in the art at the time the invention was made. Their conclusions are reasonable, and thus more credible, in view of the fact that only a single word ("preferred") in the entire eighteen columns of disclosure in the Oelrich patent is in any way contrary thereto.").

- First, at page 18 of the Office, it asserts that a person of ordinary skill in the art would read the phrase "having specificity for a particular known antigen" to mean that heavy and light chain polypeptides that can be made by the '567 claims must be assembled into an immunoglobulin to have utility. Specifically, the Office asserts that the heavy and light chains "preferably" are made for immunoglobulin assembly, and as such, "it is appropriate to construe the reference Cabilly 1 patent claims to encompass production of chimeric immunoglobulins (i.e., antibodies)..."

- Second, at page 33, the Office attempts to distinguish chimeric immunoglobulin light or heavy chains "having specificity for a particular known antigen" and those that do not, presumably under the belief that certain immunoglobulin chains do not possess amino acid sequences that enable them to confer antigen binding function when assembled into an immunoglobulin molecule or binding fragment. The Office then asserts that only "non-specific" immunoglobulins (i.e., immunoglobulins that comprise mismatched pairs of heavy and light chains from different antibodies that do not bind antigen) are useful for the diagnostic utilities referenced in the declaration of Dr. Arthur Riggs.

As explained above, whatever is disclosed in the specification of the '567 patent regarding utility of the '567 methods[16] cannot be used as prior art "knowledge" in an obviousness-type double patenting rejection. As such, the Office cannot use the teachings of the '567 patent (or its claims) to provide a motivation to modify the '567 patent claims to arrive at the '415 claims. Despite this prohibition, the Office relies on the '567 patent specification to assert that it is "reasonable to interpret the Cabilly 1 claims phrase 'immunoglobulin heavy or light chain having specificity for a particular known antigen' as suggesting the use of the Cabilly 1 claimed 'specific' immunoglobulins for assembly into antibodies." Second Office Action, page 33. The reliance on one possible utility of the '567 claims to construe the '567 claims as requiring assembly of individually produced heavy or light immunoglobulin chains into a functional immunoglobulin molecule is legally improper and factually inaccurate.

The evidence of record, including the patent specification and the Riggs Declaration, plainly demonstrates that there were well-accepted utilities for compositions of individual heavy

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[16] Indeed, the Office's view regarding the "preferred utility" of the '567 patent claims runs counter to evidence in the specification and in the record of this merged reexamination proceeding. Even if it were proper to look to the specification to ascertain what a person of skill in the art would have found "useful" about the '567 methods, the Examiner's selection from the specification of one utility (i.e., expression to facilitate "immunoglobulin assembly") among other utilities for the '567 methods ignores the separate and independent utilities of producing and using individual heavy or light immunoglobulin chains as such, as set forth in the specification and as explained in the Riggs declaration.

or light immunoglobulin chains in early April of 1983. As the '415 and '567 patent specification states:

> Finally, either the light chain or heavy chain alone, or portions thereof, produced by recombinant techniques are included in the invention and may be mammalian or chimeric. ('567 patent specification, column 5, lines 32-36, emphasis added)

Moreover, the Office appears to misunderstand substance of Dr. Riggs's declaration concerning applications of individual light or heavy chain polypeptides. As Dr. Riggs pointed out in his Declaration, purified individual heavy or light immunoglobulin chain compositions had significant commercial value in early April of 1983. He referred, by way of example, to the use of a purified individual light chain composition to raise highly specific antisera. Such antisera, in turn, could be used to detect free immunoglobulin light (kappa) chain polypeptides in fluids isolated from human patients. As Dr. Riggs explained, the presence of these free light chain proteins in the patient's fluids was a known indicator of the condition of multiple myeloma. Dr. Riggs was not suggesting, as the Office appears to believe, that "non-specific" immunoglobulins discussed in the '567 patent specification have utility in the diagnosis of multiple myeloma, while "specific" immunoglobulins (and their constituent heavy and light chains) do not.

The Office's assertion that the phrase "immunoglobulin heavy or light chain having specificity for a particular known antigen" in claim 1 of the '567 patent claims "suggests" only a use to produce functional, assembled antibodies "in contradistinction to the alternate use of non-specific immunoglobulins for the diagnosis of myeloma" thus has no basis in the specification or other evidence of record. Rather, the '567 patent claims, the shared patent specification, and the evidence of record in this proceeding (See, e.g., the Riggs declaration), demonstrate that individual heavy or light immunoglobulin chains had a well-accepted utility as of early April of 1983 that did not depend on assembly of those chains into functional, antigen-binding immunoglobulin molecules or fragments. See, e.g., ¶¶ 25-30 of the Riggs declaration. These various utilities exist independent of the whether the individual chains can confer functional antigen binding properties (e.g., by "correct" assembly with its complementary chain with the same antigen-binding specificity).

Moreover, there is nothing in the specification that suggests that when the chimeric immunoglobulin chains of the '567 patent are assembled into an immunoglobulin, the

"prefer[red]" utility is to coexpress the DNA sequences in the same cell. In fact, Dr. Riggs points out that a number of the utilities disclosed in the '567 patent specification employ expression of heavy and light chains in separate cells. See Riggs Declaration, ¶¶ 4-18. As a result, even if it was proper to import the requirement of assembly of the heavy and light chains into the '567 patent claims (which it is not), it is wholly improper to import the requirement of expressing both heavy and light chain chimeric chain encoding DNA sequences in the same cell into the claims of the '567 patent, an essential feature of only the '415 claims.

Thus, claim 1 of the '567 patent requires only that either the recovered chimeric immunoglobulin heavy chain or recovered chimeric immunoglobulin light chain alone have a particular amino acid sequence.

7. Conclusion: The Rejection of the '415 Claims Based on Claim Interpretation 1 of the '567 Claims is Factually and Legally Improper and Should Be Withdrawn

As discussed above, the '567 claims use the term "or" according to its normal meaning. The prosecution history of the '567 patent demonstrates that this interpretation was accepted and used by the Office and Owners during prosecution of the '567 patent. Because the '567 claims do not "read on" (anticipate) the later '415 claims, they do not render the '415 claims unpatentable for obviousness-type double patenting.

Accordingly, Owners respectfully request that the Office withdraw the rejections of claims 1-36 of the '415 patent based on the "Claim Interpretation 1" rationale articulated in the Office Action. Since the claims 1-7 of the '567 patent do not anticipate claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 patent (i.e., because "or" does not mean "and/or" as that term is used in the '567 claims), the rejection of the remaining '415 claims in view of additional prior art references is without foundation. Owners also invite the Office to review Owners' response to the rejections of dependent claims 5-10, 12, 14, 19-20, 22, 26-32, and 33-37 presented, infra, in section D.

C. The Rejection of Claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 Patent Based on Claims 1-7 of the '567 Patent, Taken in View of Axel, Rice or Kaplan, Further in View of Dallas, and Further in View of Deacon, Valle 1981 or Ochi is Improper

1. Obviousness-Type Double Patenting is to be Assessed in a Manner Analogous to Obviousness Assessments Under 35 U.S.C. §103 Using a Graham v. John Deere Analysis

An obviousness-type double patenting analysis is analogous to the analysis for obviousness under 35 U.S.C. §103, except that the claim of the earlier patent serves as the basis for the evaluation of obviousness. The reference claim, however, is not considered as "prior art." See M.P.E.P. § 804(II)(B)(1); General Foods Corp., 972 F.2d at 1281, 23 U.S.P.Q.2d 1839, 1846; In re Longi, 759 F.2d 887, 892, 225 U.S.P.Q. 645, 648 (Fed. Cir. 1985).[17]

Generally, an obviousness-type double patenting analysis includes three steps. First, the claims in both the earlier and later patent must be construed. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968, 58 U.S.P.Q.2d 1869, 1878 (Fed. Cir. 2001). Second, the differences between the two claims are identified. Id. Third, it must be determined whether the differences in subject matter between the two claims render the claims patentably distinct. Id. This last step requires an analysis according to the framework of Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966).[18] See M.P.E.P. § 804 (II) (B) (1); Studiengesellschaft Kohle mbH v. Northern Petrochem. Co., 784 F.2d 351, 355, 228 U.S.P.Q. 837, 840 (Fed. Cir. 1986) (holding of invalidity reversed because trial court made no findings on Graham factual inquiries to analyze obviousness-type double patenting).

The Graham analysis, as applied in an obviousness-type double patenting setting, thus requires the following factual inquiries:

(A) Determine the scope and content of a patent claim relative to a claim in the application at issue;

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[17] See also Eli Lilly & Co. v. Barr Laboratories, Inc., 251 F.3d 955, 968, 58 U.S.P.Q.2d 1869, 1878 (Fed. Cir. 2001); In re Bartfeld, 925 F.2d 1450, 1453, 17 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991); In re Braat, 937 F.2d 589, 592, 19 U.S.P.Q.2d 1289, 1292 (Fed. Cir. 1991); In re Braithwaite, 379 F.2d 594, 600, n.4, 154 U.S.P.Q. 29, 33 n.4 (C.C.P.A. 1967).

[18] In re Braat, 937 F.2d 589, 592, 19 U.S.P.Q.2d 1289, 1292 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 893, 225 U.S.P.Q. 645, 648 (Fed. Cir. 1985).

(B) Determine the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue;

(C) Determine the level of ordinary skill in the pertinent art; and

(D) Evaluate any objective indicia of nonobviousness.

See M.P.E.P. § 804(II)(B)(1) ("The conclusion of obviousness-type double patenting is made in light of these factual determinations").

Because the evaluation is to be grounded on the Graham framework, the same cautions and considerations relevant to determinations that apply in conventional obviousness determinations under §103 likewise apply in an obviousness-type double patenting setting. See id. ("A double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103' ... Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)."). For example, one purpose of the Graham framework is "to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." Graham v. John Deere, 383 U.S. at 36, 148 USPQ at 474. The "motivation" test promotes this important safeguard, which is pronounced in unpredictable fields, such as biotechnology. See, e.g., In re Kahn, 441 F.3d 977, 985-986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006).[19] Thus, to properly assess "obviousness" one must consider: (1) whether the prior art would have suggested to those of skill in the art that they should make the claimed composition or device, or carry out the claimed process; (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See Medichem, S.A. v. Rolabo, S.L, 437 F.3d

[19] The question of motivation and reasonable expectation of success in the context of biotechnology inventions in the 1980s was addressed by the Federal Circuit in In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Vaeck invented a method of transforming cyanobacteria with chimeric genes encoding insecticidal proteins. The recombinant organisms would find ready utility as insect-control agents since certain insects fed on the cyanobacteria. The Examiner rejected the claims over, inter alia, references showing the expression of heterologous genes in cyanobacteria, including the use of a chimeric "marker gene." The Examiner and Board held that it would have been obvious to substitute a gene encoding an insecticidal protein for the marker gene of the prior art, since one would have expected to successfully express the protein at high levels. The Federal Circuit reversed, noting that none of the cited references demonstrated any reason to introduce an insecticidal protein into a cyanobacterium. The mere similarity of aspects of the invention to aspects of the prior art was considered insufficient to be evidence of motivation to modify the prior art to arrive at Vaeck's invention. See generally id. at 493-494, 40 U.S.P.Q.2d at 1443.

1157 (Fed. Cir. 2006). Moreover, the question of whether the prior art does provide this motivation must be assessed using the perspective of the person of ordinary skill in the art at the time of the invention.[20]

The Office also must consider factors such as uncertainty in the field that would have led a person of ordinary skill in the art to conclude that a proposed invention would not be obvious, even if there may be some general suggestion or desire to attempt to produce the invention. See M.P.E.P. § 2145(X)(B) (citing In re O'Farrell, 53 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988) ("obvious to try" is not the standard under § 103 when exploring a "new technology or general approach"); In re Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444. And the Office must consider relevant indicia of non-obviousness. Graham, 383 U.S. at 17, 148 USPQ at 467.

2. The '415 Claims Would Not Have Been Considered Obvious to a Person of Ordinary Skill in the Art in Early April of 1983 Based on the '567 Claims, Considered Alone or in View of the Various Combinations of References Employed by the Office, When a Proper Graham v. John Deere Analysis is Employed

a. Differences Between The Claims of the '567 Patent and the Claims of the '415 Patent

The differences between the independent claims of the '567 patent and the independent claims of the '415 patent were set out in detail in Owners' response filed November 25, 2005. See First Response at pages 24 to 25, 28 to 29, 31, and Tables 2-6 of Exhibit E. Three claim elements of particular significance differentiate the '415 patent claims from the '567 patent claims.

First, the '415 patent claims require the host cell to be transformed with DNA sequences encoding at least the variable domain of the heavy chain and at least the variable domain of the light chain polypeptide. By contrast, the '567 claims require transformation of the host cell with

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[20] See McGinley v. Franklin Sports, 262 F.3d 1339, 1351-52; 60 U.S.P.Q.2d 1001 (Fed. Cir. 2001), in which the Federal Circuit held:

> For example, the level of skill in the art may inform whether the artisan would find a suggestion to combine in the teachings of an exemplar of prior art. Where the level of skill is high, one may assume a keener appreciation of nuances taught by the prior art. Similarly, appreciation of the differences between the claims in suit and the scope of prior art references-a matter itself informed by the operative level of skill in the art-informs the question of whether to combine prior art references. At bottom, in each case the factual inquiry whether to combine references must be thorough and searching.

only one DNA sequence, either a DNA sequence encoding a chimeric heavy chain or a DNA sequence encoding a chimeric light chain.

Second, the '415 patent requires that the transformed cell produce the immunoglobulin heavy and light chain polypeptides encoded by the two DNA sequences as separate molecules. This result stems from the requirement for independent expression of the introduced DNA sequences encoding the heavy and light immunoglobulin chains. The '567 patent only requires that one immunoglobulin polypeptide chain be produced in the transformed host cell.

Third, the '415 patent claims require that the processes result in an immunoglobulin molecule or an immunologically functional fragment. There is no requirement in the '567 patent claims, either implicit or explicit, that individual polypeptides resulting from the processes of those claims (i.e., a single recovered chimeric immunoglobulin heavy or light chain polypeptide) be assembled into an immunoglobulin molecule or an immunologically active fragment. As explained in Owners' First Response and summarized above, commercially significant applications existed for the individual heavy or light chain polypeptides produced by the method claimed in the '567 patent in early April of 1983, apart from using such polypeptides to assemble an immunoglobulin molecule or fragment.[21] See Riggs Declaration, ¶¶21-31; First Response, page 19.

Each of these distinctions between the '415 and '567 patent claims would have been considered significant by a person of ordinary skill in the art as of early April of 1983. The decision of the Office to simply ignore these distinctions improperly skews the "obviousness" analysis it has employed in its rejections of the '415 claims under the Claim Interpretation 2 theory, as explained below.

b. The Correct Perspective for Evaluating Prior Art is a Person of Ordinary Skill in the Art as of Early April of 1983

"Recognizing the difficulty of casting one's mind back to the state of technology at the time the invention was made, courts have long recognized the usefulness of evidence of the contemporaneous attitude toward the asserted invention. A retrospective view of the invention is

[21] For the purposes of efficiency, Owners note that various dependent claims also recite and require additional characteristics and properties beyond those required by the independent claims of the '415 patent.

best gleaned from those who were there at the time." Interconnect v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551(Fed. Cir. 1985). See also In re McKenna, 203 F.2d 717, 720, 97 USPQ 348, 350-351 (C.C.P.A. 1953) ("the courts should resort not only to an attempt to determine whether an applicant's novel feature is within the capacity of a skilled mechanic in the art, but also to the history and underlying state of the art at or about the time of the alleged invention, the occasion for it, the advantages and successes it achieves....Although there are certain obvious shortcomings in ex parte affidavits as proof, it seems to us that such affidavits are clearly one of the few practical methods of presenting a factual record sufficient to form a basis for proper application of the 'history of the art test' in this type of ex parte proceeding.") (Internal citations omitted.).

In this regard, Owners direct the attention of the Office to the Declarations under 37 C.F.R. § 1.132 of Dr. Harris and Dr. Rice submitted with this response and with the response of November 25, 2005, and the Declaration of Dr. Alan Colman submitted with the present response. Each of these declarants is able to provide accurate insights into what a person of ordinary skill in the art would have understood and expected from the cited references. These insights illustrate that many of the conclusions and findings that the Office has reached from the cited references are inaccurate. For example, in several instances, the Office concludes that a particular scientific outcome would have been "expected" based on their reading of a particular reference. In each instance, the declarants explain why the Office's finding is incorrect or inaccurate. Similarly, the Office makes numerous misstatements about what is reported in the cited references. Again, the declarants explain the error and provide relevant context. The opinions of these experts regarding what the cited references would or would not have taught a person of ordinary skill in the art in early April of 1983 is particularly relevant and insightful evidence on the question of "obviousness" and are entitled to substantial deference.

c. The Expectations of a Person of Ordinary Skill in the Art in Early April of 1983 Would Have Been Shaped by Experiences in Producing Polypeptides Using Recombinant DNA Technology, the Nature of the Protein Being Produced, and Relevant Insights from Natural Processes in B-Cells

The Office makes numerous assumptions regarding what it perceives a person of ordinary skill, in early April of 1983, would have expected based on the information contained in certain

cited references. For the reasons specifically provided below, the Office's assertions suffer from two types of flaws; namely, they are based on an inaccurate reading of the cited references, and they do not take into account the relevant factors and information that would have influenced the expectations of a person of ordinary skill at that time.

As Dr. Harris indicates, one factor that would have shaped the general expectations of a person of ordinary skill in early April of 1983 would have been the early stage of development of recombinant DNA techniques. Dr. Harris's views on that topic are set forth generally at ¶¶ 13-17 of his Second Declaration. In ¶ 13, he explains:

> In early April of 1983, the field of genetic engineering was still developing. It was nothing like the mature field it is today, over two decades later. A relatively small number of proteins had been made by recombinant DNA technology. Almost all of those were relatively simple monomeric (*i.e.*, one polypeptide chain) proteins.

See also Harris First Declaration, ¶¶ 15-19.

Importantly, Dr. Harris observes that he was not aware of any literature in that period documenting the successful production of a multimeric protein by independently expressing, in a single host cell, DNA sequences encoding the constituent polypeptides of the multimeric protein. See Harris Second Declaration, ¶¶ 14-16. Pursuant to the '415 patent, immunoglobulin molecules or immunologically functional fragments are multimeric proteins produced by independently expressing DNA sequences encoding the constituent polypeptides (e.g., the individual heavy and light chains or portions thereof) of the immunoglobulin molecule or fragment in a single host cell.[22]

Dr. Harris indicates that an important factor that would have shaped the expectations of a person of ordinary skill in the art would have been the size and structural complexity of the

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[22] Owners note that the Office attaches some significance to "functional" immunoglobulins relative to "non-functional" immunoglobulis. See, e.g., Second Office Action, page 34 (dismissing Rice First Ddeclaration observations as being directed only to "functional" immunoglobulins). The correct focus for assessing non-obviousness of the '415 claimed embodiment of immunoglobulin molecules is the proper formation of an immunoglobulin tetramer, not whether the immunoglobulin molecule is "functional" or not. According to the patent specification, a properly formed immunoglobulin tetramer made from "properly matched" heavy and light chains (chains with the same antigenic specificity) will yield an immunoglobulin that binds to the antigen. A properly formed tetramer made up of "mis-matched" heavy and light chains (chains which do not have the same antigen binding specificity chain) are unlikely to exhibit "antigen binding" function. See, e.g., '415 patent, col. 6, lines 3-11.

protein being produced. In this respect, he observes that an immunoglobulin tetramer is a large complex multimeric protein made up of four discrete polypeptides linked through a particular arrangement of disulfide bonds. See Harris Second Declaration, ¶¶ 16-18, Harris First Declaration, ¶ 17. He observes:

> Based on these known structural characteristics of the tetrameric immunoglobulin molecule, I believe a person of ordinary skill in the art, in early April of 1983, would have expected that the production of an immunoglobulin tetramer using recombinant DNA techniques would have been a significantly more challenging undertaking than the types of projects described in my review article or the molecules described in Axel et al., U.S. Patent No. 4,399,216 ("Axel") (i.e., β–globin) and Rice & Baltimore, Proc. Nat'l. Acad. Sci., 79:7862-7865 (1982) ("Rice") (i.e., a recombinant immunoglobulin light chain gene).

Harris Second Declaration, ¶ 18. Based on these points, Dr. Harris concludes at ¶ 20 of his Second Declaration that:

> I also do not believe a person having ordinary skill at that time would have many expectations regarding a project of the scale of the '415 patent process based solely on their knowledge of general techniques for producing polypeptides in host cells transformed with recombinant DNA sequences.

See also Harris First Declaration, ¶ 16; Rice First Declaration, ¶ 15; Rice Second Declaration, ¶ 52.

Dr. Harris and Dr. Rice also provide their views on the significance of work that had been done by early April of 1983 involving expression of light chain genes in cell lines of B-lymphocyte lineage. Their statements correct the inaccurate views expressed by the Office as to the significance of the results reported in the Rice, Ochi and Oi papers to the '415 claims.

Initially, as both Dr. Rice and Dr. Harris indicate, a person of ordinary skill in the art would have assessed the significance of the experimental results reported in Rice, Ochi and Oi in light of the literature available at the time documenting factors affecting the ability of B-cells to produce and secrete immunoglobulin tetramers. For example, it was known in early April of 1983 that the processes governing how B-lymphocytes produce immunoglobulin tetramers were complicated and influenced by a number of interrelated factors. See Harris Second Declaration, ¶¶ 22-27; Rice Second Declaration, ¶¶ 10-16. Similarly, it was believed that the ability of a B-

lymphocyte to successfully produce an assembled immunoglobulin tetramer was dependent not only on whether the heavy and light chain polypeptides had been produced in the B-cell, but also on the timing and levels of expression of the light and heavy chain genes in the cell, as well as other factors. As Dr. Harris explains:

> Thus, research that had been done by early April of 1983 had shown that a number of independent but interrelated factors could affect the successful production of the immunoglobulin by the B-lymphocyte including:
>
> (i) The timing and levels of expression of messenger RNA from the native immunoglobulin genes in the B-lymphocytes,
>
> (ii) The amount of heavy and light chain polypeptides present in the cell at various times and locations (*i.e.*, the "stoichiometry" of polypeptides in the cellular environment where the immunoglobulin tetramer might be formed),
>
> (iii) The developmental state of the B-lymphocyte (*e.g.*, whether it had gained the capacity through its development to express the immunoglobulin genes at appropriate levels, or could process the gene expression products to form the immunoglobulin tetramer), and
>
> (iv) The presence of agents in B-lymphocytes that facilitated proper assembly and secretion of the tetrameric immunoglobulin molecule (so-called "helper" proteins).

See Harris Second Declaration, ¶ 27; see also Rice Second Declaration, ¶ 16.

It also is important to appreciate that, despite the extensive amount of work that had been done by that time to document B-cell behavior, little was known in early April of 1983 about how these processes actually worked. As Dr. Rice explains:

> ... the processes that control immunoglobulin gene rearrangement and expression were not understood at that time, as we indicated in our 1982 *PNAS* paper (*see*, page 7862, left column). The unusual complexity of this system would have caused a person of ordinary skill in the art at that time to question whether one could achieve successful expression of exogenous light and heavy chain DNA sequences in a B-lymphocyte without disrupting the ability of that cell to properly express the introduced sequences, or carry out post-transcriptional events, such as immunoglobulin polypeptide folding, assembly or secretion.

See Rice Second Declaration, ¶ 13. Similarly, Dr. Harris noted that:

> ... the literature had shown that the processes that govern the assembly and expression of immunoglobulin genes were unique compared to other types of genes. Immunoglobulin genes are assembled by rearrangement of gene fragments in the B-cell incidental to the cell's development into mature, immunoglobulin secreting plasma B-cells. The factors that controlled or influenced the processes of B-cell development as well as the assembly and expression of immunoglobulin genes, however, were not understood by early April of 1983.

See Harris Second Declaration, ¶ 23. Indeed, Dr. Harris points to the introduction of Rice as evidence that this description was the prevailing view at the time. See Harris Second Declaration, ¶ 24.

This was also the case with respect to the post-expression events in the B-cell (e.g., the processes governing folding, assembly and secretion of the immunoglobulin tetramer). As Dr. Rice explains at ¶ 14 of his Second Declaration:

> Similarly, the processes governing immunoglobulin assembly and secretion in B-lymphocytes were not understood in April of 1983. Instead, it was known from studies involving cultures of B-lymphocyte cells, such as hybridomas or myeloma lines, that production and secretion of intact immunoglobulin tetramers were subject to many unknown and uncharacterized variables. For example, at that time there were numerous reports in the literature of hybridoma and myeloma cell lines that, during the passage of these cell lines over time, spontaneously lost the ability to express their immunoglobulin genes, produce individual heavy or light chains, or secrete immunoglobulin tetramers. *See*, *e.g.*, Coffino et al., *PNAS* 68:219-223 (1971) (attached as Exhibit C). Some researchers also reported that excess amounts of free heavy chain in mutant hybridoma lines often was toxic to these cell lines. *See*, Kohler, *PNAS* 77:2197-2199 (1980) (attached as Exhibit D). Excess free heavy chain can result from loss of the light chain gene, inadequate expression of the light chain gene or imbalances in amounts of the individual immunoglobulin chains caused by factors in the cellular environment.

See also Harris Second Declaration, ¶¶ 25-26. Dr. Harris also notes that this information "would have caused a person of ordinary skill to question whether unbalanced or uncontrolled production of heavy chain and light chain polypeptides in a transformed host cell would be toxic to the cell." See Harris Second Declaration, ¶ 25.

Thus, a person of ordinary skill in the art in early April of 1983, considering the '567 patent claims, and the various references cited by the Office, would have understood that:

(i) The processes governing immunoglobulin gene rearrangement, expression, as well as assembly of the light chain and heavy chain products, were considered to be very complex, affected by numerous factors and not well characterized.

(ii) Recombinant technology was in its infancy, in particular as it related to the expression and assembly of multimeric proteins.

As such, a person of ordinary skill in the art in early April of 1983 would have interpreted the results reported in Rice, Ochi and Oi conservatively, not expansively as the Office has done. Simply put, in early April of 1983, the cited references would not have led a person to "reasonably expect" that a host cell transformed with exogenous DNA sequences encoding the heavy and light immunoglobulin chains would properly assemble immunoglobulin tetramer, or that a host cell transformed in this manner would successfully assemble an immunoglobulin tetramer simply because heavy and light polypeptides were present in the cell.

d. The Office May Not Disregard Pertinent Expert Testimony Correcting Erroneous Interpretations of the Teachings of the Prior Art

In the first and second Office Actions, the Office makes a number of specific findings regarding what would have been taught by Axel, Rice, Kaplan and other references in early April of 1983. The Declarations provided by Drs. Harris, Rice and Colman explain why these findings are inaccurate or incorrect. Each of the declarants analyzed the observations and explanations provided by the Office concerning some or all of the cited references. Each declarant identified numerous findings and statements of the Office that do not accurately portray what these references actually would have taught one of ordinary skill in the art in early April of 1983, or what such a person would have reasonably expected based on those teachings at that time.

At pages 33-34 of the Second Office Action, the Office appears to dismiss certain observations of Drs. Harris and Rice set forth in their respective First Declarations submitted under 37 C.F.R. §1.132, stating "it is noted that in response to patentee's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references" The Office cites In re Keller, 642 F.2d 413, 208 U.S.P.Q. 871 (C.C.P.A. 1981) and In re Merck & Co., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986) to support its position.

The content of the prior art cited to support an obviousness analysis is a question of fact. In re Dembiczak, 175 F.3d 994, 998, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999). In this regard, the opinions of qualified experts as to the technical content of the cited references constitute highly relevant evidence into how those references would be understood by one of ordinary skill in the art at the time of the invention. See In re Bulina, 362 F.2d at 557-558, 150 USPQ at 112-113 (C.C.P.A. 1966).[23] Indeed, the Office is obliged to take such evidence into account and assess obviousness anew whenever such evidence is presented. In re Eli Lilly & Co., 902 F.2d 943, 14 U.S.P.Q.2d 1741 (Fed. Cir. 1990); see also M.P.E.P. § 2142.

The cases cited by the Office do not hold that the Office may disregard testimony of qualified scientific experts that corrects the Office's mischaracterization of scientific facts and findings. These cases also do not suggest that the Office can simply dismiss relevant scientific insights of qualified experts who elect to explain what a particular reference would have taught a person of ordinary skill in the art at the relevant time. As the cases cited by the Office actually acknowledge, expert testimony on what a reference would have taught a person of ordinary skill in the art at the relevant time is to be accorded substantial deference by the Office. See Keller, 642 F.2d at 426, 208 U.S.P.Q. at 882 ("In Carroll this court concluded that the opinion of an expert on what the prior art taught was deserving of considerable deference under the circumstances of that case. The expert had critically reviewed the sole piece of prior art and totally discounted its value. The accuracy of the expert's views was supported by documentary evidence.").[24] And, of course, an obviousness rejection based on a combination of references necessarily rests upon the factual determination of what each of the prior art references would have taught a person of ordinary skill in the art at the relevant time. See M.P.E.P. § 2141.I, quoting Graham v. John Deere, 383 U.S. at 17, 148 U.S.P.Q. at 467 (1966) ("Under §103, the

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[23] As the Federal Circuit held:

> The factual issue to be resolved as to the patentability of claims 1 to 7 and 11 and 12 in view of Cochardt first requires an understanding of the Cochardt teachings.... To support a finding of obviousness under section 103 it is essential that it be based on a sound factual basis. We have reviewed the Conrad affidavit which the board refused to consider and find it persuasive indeed that the assumptions or inferences of scientific fact which the board found in the Cochardt reference are not supportable.... The board's refusal to consider the affidavit of Conrad under the circumstances of this case was erroneous. It should have carefully considered the affidavit since the introduction of the affidavit was occasioned by what appears to be the board's extrapolation of unsupported facts from the teachings of Cochardt.

[24] See In re Carroll, 601 F.2d 1184, 202 U.S.P.Q. 571 (C.C.P.A. 1979).

scope and content of the prior art are to be determined. ... Against this background, the obviousness or nonobviousness of the subject matter is determined.")

Notwithstanding this, Owners note that Dr. Harris addresses in his Second Declaration how the '567 claims would have been considered by a person of ordinary skill in the art in view of each of the primary references, Axel, Rice, and Kaplan (paragraphs 48, 67, 70), as well as in view of the secondary reference, Dallas (paragraph 78), further in view of the tertiary references, Ochi, Deacon, and Valle 1981 (paragraphs 86 and 97). and, finally, in view of Builder and Accolla (paragraphs 98-100). The Second Declaration of Dr. Rice and Declaration of Dr. Colman provide a detailed analysis of the references addressed to their core expertise (for Rice, his 1982 PNAS paper, and the counterpart Ochi and Oi papers, and for Colman, his Valle 1981 and Valle 1982 papers, and the Deacon paper). Each of these authors read and considered in context all of the references cited by the Office.

e. The Office's Rejection of the '415 Claims Based on the '567 Claims Taken in View of the Various Cited References Rests on a Flawed and Incorrect Analysis of the Claims and the Teachings of the Cited References

The rejection of claims 1-36 of the '415 patent based on the claims of the '567 patent, taken in view of various combinations of cited references suffers from three significant flaws.

- First, as explained earlier, the Office overlooks significant distinctions that exist between the '415 and '567 claims, and oversimplifies the questions implicated by these distinctions.
- Second, the Office improperly characterizes what the cited references would have taught a person of ordinary skill in the art in early April of 1983. This is reflected in findings and statements the Office makes about the contents of the cited references.
- Third, the Office imbues into the person of ordinary skill in the art in early April of 1983 far more insight and knowledge than is warranted. This leads the Office to make numerous errors in characterizing what a person of ordinary skill in the art would have "reasonably expected" at the time.

As a result of these errors, the Office advances two critical "findings" that it relies upon to reject all of the claims of the '415 patent as being unpatenable for "obviousness-type" double patenting reasons, in view of cited references; namely:

(i) One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference '567 patented invention in light of Axel, Rice, Kaplan and Dallas; and

(ii) Deacon, Valle 1981, and Ochi provide further motivation to make active antibody with a reasonable expectation of success.

Neither of these assumptions of the Office is supported by the actual contents or teachings of the cited references. Moreover, neither assumption is consistent with the expectations a person of ordinary skill in the art would have had in early April of 1983 based on an accurate reading of the cited references, and in view of their general knowledge and experience.

On the first point, the Office asserts that a person of ordinary skill in the art in early April of 1983 would have found a direct suggestion in Axel and Rice (and possibly Kaplan), considered alone or further in view of Dallas, to modify the '567 patent claims to "transform a single host with:

a. the individual Cabilly 1 vectors separately containing a light or heavy chain; or

b. a modified Cabilly 1 vector encoding both an immunoglobulin light and heavy chain for independent expression of these chains."

Second Office Action, page 24.

As explained below, none of the cited references – Axel, Rice, Kaplan, or Dallas – actually states or suggests what the Office asserts. Indeed, it is striking that not one of these references expressly states that the work being described in the reference might somehow be relevant to producing immunoglobulin molecules or functional fragments by independently expressing, in a single host cell, DNA sequences encoding both light and heavy immunoglobulin chains. If what the Office asserts were true, one would expect that at least one of the references would have expressly made this point, at least in passing. See Rice Second Declaration, ¶ 32.

The Office's characterization of Axel, Rice, Kaplan and Dallas also is inconsistent with how a person of ordinary skill in the art would have read these references, as is explained below. As Drs. Harris and Rice explain in their declarations submitted with this response, none of Axel, Rice, Kaplan or Dallas, read accurately, specifically suggests producing a multimeric protein by

independently expressing DNA sequences corresponding to the constituent polypeptides of the protein in a single host cell. Indeed, as they explain, when the Axel, Rice and Kaplan disclosures are read properly, they actually teach nothing more than what is already required by the '567 claims (i.e., producing one immunoglobulin chain polypeptide in a host cell transformed with a DNA sequence encoding one immunoglobulin polypeptide).

Dallas does nothing to remedy the shortcomings of any of Axel, Rice or Kaplan, as it does not provide any direction or suggestions to a person of ordinary skill concerning how to express two complex eukaryotic proteins in a single transformed host cell. As a result, Axel, Rice, and Kaplan, considered individually or in combination with Dallas, do not provide any motivation to a person of ordinary skill in the art to modify the '567 claims to arrive at what is required by the '415 patent claims. The Office's erroneous interpretation of the teachings of these references directly affects the basis of its assertions that the '415 claims are obvious over the '567 claims, and thus are unpatentable for obviousness-type double patenting.

For analogous reasons, the Office is incorrect when it suggests that the Deacon, Valle 1981 and Ochi references would have led a person to reasonably expect success in the production of an immunoglobulin molecule or fragment via the independent expression of DNA sequences encoding the heavy and light immunoglobulin chains (or portions thereof). The Deacon and Valle 1981 references concern experiments involving injection of mRNA fractions into oocytes from Xenopus (the South African clawed frog). These experiments do not provide findings that would be representative of what might be seen in host cells transformed with exogenous DNA sequences encoding heavy and light immunoglobulin chains. For example, Dr. Alan Colman, co-author of the Valle 1981 and Valle 1982 publications, explains that the Xenopus oocyte is a unique type of cell with capabilities and attributes that are not characteristic of host cells. He also explains why, contrary to the assertions of the Office, experiments involving translation of mRNA fractions in Xenopus oocytes implicate significant distinctions relative to results that might be obtained through transformation of host cells with exogenous DNA sequences.

Ochi discloses findings analogous to those reported in Rice. Like Rice, Ochi describes an experiment where a lymphoid cell line (a hybridoma) that is expressing one or more immunoglobulin heavy and light chain genes was transfected with a rearranged immunoglobulin

light chain gene. Indeed, as Dr. Rice explains, the experimental design of the Ochi work is more limited than the model reported in his paper. This, among other things, operates to constrain the expectations that a person of ordinary skill in the art would have had as to how the Ochi work might have been viewed or extended in early April of 1983.

As a consequence, none of Deacon, Valle 1981 or Ochi support the assertions of the Office that these publications "provide further motivation" to modify the '567 claims, because one of ordinary skill in the art would not have had a reasonable expectation, based on these publications, that one could successfully transform a single host cell with exogenous DNA sequences encoding the heavy and light chains, cause the host cell to express both sequences, and achieve production of immunoglobulin molecules or functional fragments.

Because the references considered together would not have rendered obvious the production of an immunoglobulin tetramer by transforming a single host cell with DNA sequences corresponding to the heavy and light chains of the immunoglobulin, there is no proper basis for the rejection of claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of the '415 patent as set forth by the Office.

(i) The Axel Patent Does Not Motivate One to Produce Heavy and Light Chains in a Single Transformed Host Cell

The Office asserts that (i) Axel teaches that its processes are particularly suited for the transformation of eukaryotic cells with DNA to make antibodies, and (ii) that Axel discloses and claims the expression of antibodies in mammalian hosts as "intact (assembled)" proteins. See Second Office Action, pages 22-23. The Office relies on this finding to assert that a person of ordinary skill, taking account of Axel (or Axel together with Dallas, addressed below), would have been motivated to transform a host cell with either two vectors (one containing a DNA sequence encoding a heavy chain and the other containing a DNA sequence encoding a light chain), or with one vector that contains DNA sequences encoding both the heavy and light chains.

The Office's assertions regarding what Axel would have taught or suggested to a person of ordinary skill in the art in early April of 1983 are incorrect. As Dr. Harris explained in his first declaration, Axel does not describe processes for producing more than one polypeptide of

interest in a single transformed host cell.[25] See Harris First Declaration at ¶¶ 22-25. Instead, Axel describes a method in which a eukaryotic cell is transformed with:

- a first DNA sequence encoding a "proteinaceous material" that is produced by and isolated from the transformed host cell (i.e., "DNA I") and
- a second DNA sequence encoding a selectable marker—a genetic tag allowing one to easily identify a successfully modified cell but which is not itself isolated from the transformed host cell (i.e., "DNA II").

See Harris First Declaration, ¶¶ 21-24, Harris Second Declaration, ¶ 38. Because Axel does not teach or suggest production of multiple distinct "desired" polypeptides in a single cell through expression of multiple different DNA sequences encoding such distinct polypeptides, it cannot be portrayed as providing a motivation to modify the '567 patent claims. Instead, as Dr. Harris points out, Axel teaches nothing more than what is inherently required by the '567 patent – production of one polypeptide (i.e., a heavy or a light immunoglobulin chain polypeptide) in one transformed host cell. See Harris Second Declaration, ¶¶ 39, 44, 48.

The Office responds to Dr. Harris's first declaration by referring to passages in Axel that the Office asserts present a contrary view. Specifically, the Office points to the word "antibody" as it appears in various sections of the Axel specification and in certain claims of Axel. The Office asserts that these passages demonstrate that (i) Axel discloses and claims the expression of antibodies in mammalian hosts "as intact (assembled) proteins", and (ii) Axel suggests expressing two immunoglobulin chains in a single cell "since Axel discloses and claims (e.g., claim 7) DNA (i.e., DNA 1) encoding an antibody that necessarily possesses both heavy and light immunoglobulin chains." The Office attempts to bolster its assertion by pointing to a reference to plural "genes" in the Axel abstract. See Second Office Action, pages 23, 34. The Office suggests this means that Axel is providing an explicit suggestion to express DNA sequences encoding the heavy and the light immunoglobulin chains in a single transformed host cell. Owners respectfully disagree, as Axel, read accurately, does not support the Office's assertions.

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[25] In Axel, the polypeptide that is sought to be isolated from the transformed cells is encoded by DNA I, while a second polypeptide encoded by DNA II is the marker, which is not isolated as the protein of interest.

First, Dr. Harris explains that after a thorough review of the Axel disclosure, he was unable to find any reference to "intact" or "assembled" antibodies. See Harris First Declaration ¶28; Harris Second Declaration, ¶47. He also indicates that if Axel meant to teach production of "intact (assembled)" antibodies through co-expression of light and heavy chains in one host cell the patent would have included, at least in passing, some acknowledgement that the antibody is a tetrameric protein that would have to be somehow assembled out of multiple constituent polypeptides. See Harris Second Declaration, ¶47. But, as he indicates, "[t]here is none."

Second, Dr. Harris disagrees with the Office that the mere use of the word "antibodies" in the specification or claims, or the reference to plural "genes" in the Axel abstract, necessarily means that Axel is specifically suggesting expression of DNA sequences encoding heavy and light immunoglobulin chains in a single transformed cell. See Harris Second Declaration, ¶¶ 44-45. For example, Dr. Harris explains that the portions of the Axel specification cited by the Office would not be read by a person of ordinary skill in the art as suggesting that the Axel process is "particularly" suited for making assembled antibodies any more than it suggests that the Axel process is "particularly" suited for making any other type of polypeptide. See Harris Second Declaration, ¶ 42. Dr. Harris further explains that the laundry list of molecules (i.e., "interferon protein, insulin, growth hormones, clotting factors, viral antigens, antibodies and certain enzymes") found in the referenced sections of Axel simply identifies types of proteins having potential economic value at the time the Axel patent was filed, and would not be read by a person of ordinary skill in the art as making a specific suggestion to produce the heavy and light chains of the antibody in a single transformed host cell. See Harris Second Declaration, ¶42. Indeed, under the Office's reasoning, the production of any molecule coming within the Axel laundry list would be "obvious," a result that is clearly not supportable.

Dr. Harris similarly finds that the inclusion of the word "antibody" in claim 7 does not convey any particular suggestion about expressing two DNA sequences in a single transformed host cell. See Harris Second Declaration, ¶¶ 43-44. He indicates the alternative references to "viral antigen" and "antibody" in that claim actually reinforces his opinion that it does not. See Harris Second Declaration, ¶43. For example, he points out that viral antigens do not have a characteristic or uniform polypeptide structure like an immunoglobulin tetramer. See Harris Second Declaration, ¶ 43. As he states:

> I do not believe a person of ordinary skill in the art would have referred to these classes of polypeptides in the alternative if they were intending to convey a particular observation about the multimeric nature of the antibody molecule.

Harris Second Declaration, ¶43.

Third, Dr. Harris explains that the references to plural "genes" in Axel does not refer to transfection of host cells with multiple DNA sequences encoding different polypeptides of interest.[26] See Harris Second Declaration, ¶ 45. As Dr. Harris explains, this reference to "genes" is connected to the idea of producing a transformed host cell having multiple copies of the same DNA sequence encoding the same single desired polypeptide, by which process "multiple copies of proteinaceous or other desired molecules can be produced within eukaryotic cells." Harris Second Declaration, ¶ 46 (citing column 7, lines 32-34, of Axel). In particular, Dr. Harris points to passages in the Axel specification (e.g., column 6, line 44 to column 7, line 45; column 14, lines 16-18) that explain that one can introduce multiple copies of genes in a host cell either by inserting multiple copies of the desired gene, or by inserting a construct that will amplify and thus produce multiple copies of the same DNA sequence with selection pressure (e.g., methotrexate). See Harris Second Declaration, ¶ 46. The latter method, of course, will simply replicate the introduced DNA sequence. The presentation in the Axel patent of these as alternative means of achieving the same end (multiple copies of the DNA sequence in the transformed host cell) plainly is contrary to the Office's interpretation of this portion of the Axel abstract.

All of these observations lead Dr. Harris to conclude that the Office Action is incorrect when it suggests that Axel specifically suggests producing multiple distinct polypeptides, particularly heavy and light immunoglobulin chains, by expressing DNA sequences encoding these distinct polypeptides in a single transformed cell line. See Harris Second Declaration, ¶¶ 40, 44, 45, 48; Harris First Declaration, ¶¶ 25, 29-30.

Dr. Harris also explains that nothing else in Axel supports the Office's view that its process is "particularly suited" for production of a multimeric immunoglobulin molecule. See

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[26] That interpretation of Axel is necessary to support the Office's assertions that the Axel process specifically teaches production of intact antibodies, because only that interpretation leads to the possibility that two different polypeptides (i.e., the heavy and light chains of the immunoglobulin) would be produced by the Axel process.

Harris Second Declaration, ¶42. As he explains, Axel does not place any particular emphasis on antibody production relative to any other type of polypeptide. See Harris Second Declaration, ¶ 42. Dr. Harris also did not find any specific reference to procedures uniquely relevant to production of antibody tetramers. See Harris First Declaration, ¶¶ 27-28; Harris Second Declaration, ¶¶ 39, 43, 47. Dr. Harris explains that the use of the word "antibody" certainly does not convey the suggestion of the production of intact tetramers. See Harris Second Declaration, ¶ 47. Similarly, the only actual experiments described in Axel (columns 9-42) in which a mammalian protein of interest is encoded by DNA I concern β-globin. As noted in the Harris declaration, ¶ 39, this is a much smaller and less complex polypeptide relative to the immunoglobulin tetramer (about 16kD vs. 150kD). Based on his observations, a person of ordinary skill would not have found in Axel any direct or implicit suggestion to modify the '567 patent claims to yield processes where both heavy and light immunoglobulin chains are produced in a single transformed cell line. See Harris Second Declaration, ¶ 48.

As a scientist actually working in the field of the invention in early April of 1983, Dr. Harris's views of what Axel would have taught to a person of ordinary skill in early April of 1983 are entitled to significant weight. Interconnect, 774 F.2d at 1138, 227 U.S.P.Q. at 547; see also In re Zeidler, 682 F.2d at 967 (C.C.P.A. 1982) (Board committed reversible error in "substitut[ing] its judgment for that of an established expert in the art" to assess obviousness).

Thus, because Axel does not suggest or teach production of both heavy and light immunoglobulin chains in a single transformed host cell, it adds nothing beyond what is implicit in the claims of the '567 patent (i.e., production of one immunoglobulin polypeptide in one transformed host cell). As Dr. Harris observes, Axel "is concerned with transformation of a eukaryotic cell with a DNA encoding a single recombinant protein (or multiple copies of that single DNA) in one transformed host cell." Harris Second Declaration, ¶ 48. Dr. Harris further notes that the "process of producing one Ig chain in one cell" is the '567 patent process. See Harris Second Declaration, ¶ 48. Axel cannot be portrayed as motivating a person of ordinary skill in the art to modify the '567 claims to yield the '415 patent claims, because it adds nothing beyond what is already required by the '567 patent claims. Rejections predicated on the view that Axel teaches otherwise are factually and legally flawed, and should be withdrawn.

(ii) Because Rice Describes Expression of One Exogenous Gene in One Host Cell, It Would Not Have Motivated a Person of Ordinary Skill in the Art to Modify the '567 Claims

The Office asserts that "Rice demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins."[27] See Second Office Action at page 23. Owners respectfully disagree that a person of ordinary skill in the art, in early April of 1983, would have read Rice in this manner.

As was the case with Axel, the Office has improperly relied on an unsubstantiated characterization of what Rice would have taught a person of ordinary skill in early April of 1983. Owners have provided Declarations of Dr. Douglas A. Rice (the first author of Rice) and Dr. Timothy Harris, each of whom each explain why the Office's characterization of what Rice would have taught a person of ordinary skill in the art in early April of 1983 is incorrect or inaccurate.

Both Dr. Rice and Dr. Harris explain that the Office has incorrectly and improperly equated the observation in Rice that the κ-2 line "expressed" its heavy chain gene and "successfully expressed" the introduced exogenous light chain gene to conclude that Rice "demonstrat[es] successful expression of heavy and light immunoglobulin genes in one host cell." See Rice Second Declaration, ¶¶ 27-28; Harris Second Declaration, ¶¶ 61-62. As Dr. Rice explains:

> The PTO fails to make a critical distinction between the normal continued expression of an endogenous heavy chain gene by this cell line and the introduction and "successful expression" of the functionally rearranged exogenous light chain gene that was described in the paper. The "success" in our work was the introduction and subsequent expression of the exogenous light chain gene. We did not introduce a heavy chain gene into the cell. We also made no effort to specifically control expression of the endogenous heavy chain gene (other than by providing a general cellular

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[27] The Office also states (in response to the declarations of Dr. Rice and Dr. Harris submitted with the First Response) that:

> ... the Rice reference clearly teaches to one of ordinary skill in the art that an exogenous immunoglobulin light chain assembles with a heavy chain endogenously produced by the cell even though both chains possess different antigen specificity. Thus, in light of this teaching it would be reasonable for one of ordinary skill to expect that expressing a light and heavy chain of the same antigen specificity (e.g. derived from a known antibody) would result in assembly of a functional antibody.

> transcriptional stimulus via incubation of the transfected cells with lipopolysaccharide) (see, page 7865).

Rice Second Declaration, ¶ 28. This leads Dr. Rice to conclude:

> I do not believe a person of ordinary skill in the art in early April of 1983 would have considered our observation in the 1982 PNAS paper that the 81A-2 cell line continued its expression of its endogenous heavy chain gene to be relevant to the question of whether one could achieve expression of an introduced heavy chain gene and an introduced light chain gene. In fact, even by early April of 1983, I was not aware of any experiments in the scientific literature where expression of an exogenous heavy chain gene had been demonstrated in a stably transformed lymphoid cell line.

Rice Second Declaration, ¶ 29. Dr. Harris similarly observes that:

> In my opinion, a person of ordinary skill in the art in early April of 1983 would have distinguished successful expression of a recombinant DNA sequence introduced into a lymphoid cell from "natural" expression of an endogenous gene by a B-cell. Expressing a recombinant DNA sequence in a host cell requires that one transfect the cell and successfully cause the cell to express the inserted sequence. The natural expression by a cell of one of its endogenous genes does not require one to perform these steps.

Harris Second Declaration, ¶ 61.

The distinction is thus a significant one. In early April of 1983, a person of ordinary skill in the art would have known that production of immunoglobulin tetramers by lymphoid cells, such as the 81A-2 and κ-2 lines described in Rice, was a complex process affected by many interrelated factors. See Rice Second Declaration, ¶¶ 11-16; Harris Second Declaration, ¶¶ 22-28, 51-53. Among those factors were the timing and levels of expression of the endogenous heavy and light chain genes in the cell. See Rice Second Declaration, ¶¶ 12-13; Harris Second Declaration, ¶¶ 27, 52. For example, it was known that unbalanced expression of the two immunoglobulin genes in a lymphoid cell could affect the production of the immunoglobulin polypeptides by that cell, as well as the subsequent folding, assembly and secretion of the immunoglobulin tetramer, among other events. See Rice Second Declaration, ¶¶ 14-15; Harris Second Declaration, ¶¶ 25, 27, 63. Moreover, some noted researchers (Kohler, Milstein) had reported that excess production of free heavy chain could prove toxic to hybridomas. See, e.g., Harris Second Declaration, ¶25; Rice Second Declaration, ¶14. As such, a person of ordinary

skill in the art, in early April of 1983, would have considered the control of expression of the heavy and light chain encoding DNA sequences to be important in a cell line such as the lymphoid line used in Rice. See Harris Second Declaration, ¶¶ 52-53.

Despite this, as both Dr. Rice and Dr. Harris explain, Rice does not explain how to control expression of exogenous immunoglobulin heavy and light chain genes in lymphoid cells.[28] For example, Dr. Harris points out that Rice does not fully characterize the functionally rearranged light chain gene used to transfect the κ-2 line. See Harris Second Declaration, ¶ 54, 57 to 58. He also notes that Rice indicates that the expression observed in the paper appears to be controlled by factors that had not been characterized. See Harris Second Declaration, ¶ 52. Dr. Harris observes that

> In Rice, the authors did not insert a well-defined DNA sequence encoding only the immunoglobulin light chain into the cell. Instead, they inserted a piece of genomic DNA that contained several uncharacterized sequences beyond the sequence of the light chain. These included the intervening sequence between the sequences coding for the variable (Vk), joining (Jk) and constant (Ck) regions, and about 1-1.5 kb of DNA on either side of the light chain sequence. The authors noted that "any of this extra DNA could be involved in promoter and control functions," suggesting that more than just the DNA sequence of the light chain is required for expression. (*See* page 7865.) They also noted that the rearranged light chain gene "apparently" used its own promoter to control expression, rather than the standard promoter selected and inserted by the authors of the Rice paper. The promoter that caused expression was not identified or characterized. (See page 7865.)

Harris Second Declaration, ¶ 54.

Indeed, the authors of Rice state that it was an "open question" whether the ongoing endogenous heavy chain expression was controlling or otherwise affecting the expression of the introduced light chain gene. See Harris Second Declaration, ¶ 55. Rice also did not attempt to explain the mechanisms that controlled expression of the light chain gene used to transform their

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[28] This is also a problem observed in the Ochi and Oi papers. In Ochi, levels of expression of an anti-TNP light chain gene in a mutant hybridoma were ten times lower than normal levels than the parental line. See Rice Declaration, ¶24. The variation in Oi is even more pronounced. The authors report widely varying levels of expression in their transformants, ranging from negligible to levels approximating endogenous light chain expression levels. See Rice Declaration, ¶¶ 23-24. The variability was even observed when the same light chain gene was used to transform the same variant lymphoid line. See Rice Declaration, ¶24.

lymphoid cell line, which, as the authors of Rice acknowledge, remained a topic of ongoing research. See Rice Second Declaration, ¶¶ 19-20.

These types of observations in the Rice paper fundamentally undercut the Office's assertions that Rice would have provided a broadly applicable teaching of how to express multiple immunoglobulin genes in a single host cell. Indeed, Rice does not even discuss extension of its experimental system to procedures for expression of exogenous DNA sequences encoding both the heavy and the light chain in a single host cell. See Rice Second Declaration, ¶¶ 32, 55-56; Harris Second Declaration, ¶¶ 57-62.

Similarly, the work described in Rice only concerned transfection of cell lines of the B-lymphocyte lineage. As Drs. Rice and Harris both explain, a person of ordinary skill in the art, aware of the complexity and unique characteristics of B-lymphocytes, would not have extended these limited examples involving B-cells broadly, either to other lymphocytes or to other types of host cells. For example, as Dr. Rice explains at paragraph 26 of his Second Declaration:

> Accordingly, I do not believe a person of ordinary skill would have extended the limited experimental results in these three papers in the way the PTO suggests at pages 23-26 and 34-35 of the Second Office Action. Specifically, I do not believe the 1982 *PNAS*, *Ochi* and *Oi* papers would have led a person of ordinary skill in the art to expect that introducing heavy and light chain genes into a B-lymphocyte cell line would result in successful expression of the genes, or production and secretion of intact, properly formed immunoglobulin tetramers. In my opinion, these papers certainly would not have led such a person to reach an even more aggressive scientific prediction; namely, that any host cell transformed with exogenous DNA sequences encoding heavy and light chain polypeptides would reasonably be expected to successfully express the introduced sequences, and produce properly formed immunoglobulin tetramers.

Similarly, Dr. Harris observes:

> The picture all this work painted was that the expression of immunoglobulin genes in B-lymphocytes, and the natural processes governing production and secretion of tetrameric immunoglobulin molecules by these cells, was complicated and influenced by many interrelated variables. To the extent that a person of ordinary skill in the art turned to the work involving B-lymphocytes for guidance, that person would have reached the conclusion that successful co-expression of recombinant heavy and recombinant light chain DNA sequences in a

> single host cell, and assembly of immunoglobulin tetramers following co-expression of the introduced sequences, would have been dependent on many interrelated factors. Such a person would not have expected the task to have been as straightforward or predictable as the Office suggests it was in early April of 1983.

Harris Second Declaration, ¶ 28.

The Office also overstates the experimental findings found in Rice. For example, the Office asserts that Rice "clearly teaches" that "an exogenous immunoglobulin light chain assembles with a heavy chain endogenously produced by the cell … ." This statement ignores the substantial differences that a person of ordinary skill in the art would have viewed between expression of exogenous heavy and light chain genes relative to expression of one exogenous light chain gene in a B-cell that was already expressing its endogenous heavy chain gene. See Rice Second Declaration, ¶ 29; Harris Second Declaration, ¶ 59. This specialized B-lymphocyte cell line, according to Dr. Rice, "was 'poised' to express an introduced exogenous light chain gene." Rice Second Declaration, ¶ 31. As Dr. Harris observed in ¶ 62 of his Second Declaration:

> This observation [of expression of the exogenous light chain gene with continued expression of the endogenous heavy chain gene] in Rice also does not suggest what might happen if their transformed lymphoid cell were to be transformed with a recombinant DNA sequence encoding a heavy chain polypeptide in addition to the recombinant light chain gene. Given the uncertainty expressed in the paper about what factors contributed to the successful expression of the recombinant light chain gene, I do not believe a person of skill in the art would have jumped to the conclusion that one could introduce two immunoglobulin genes into the same cell and achieve successful expression of both sequences. The authors of the paper, for example, did not make any suggestion along these lines.

Moreover, the Office overlooks the fact that Rice actually contains very little information in it that characterizes the expression products of the cell. For example, Dr. Harris points out that the test data characterizing the expression product was not actually provided in the publication. See Harris Second Declaration, ¶ 64. Accordingly, Dr. Harris does not consider Rice to amount to the "clear demonstration" of proper immunoglobulin assembly that the Office suggests. See Second Harris Declaration, ¶ 64.

Simply put, Rice would not have been read by a person of ordinary skill in the art in early April of 1983 as the Office suggests. See Rice Second Declaration, ¶ 27; Harris Second Declaration, ¶ 51, 58, 60. Rice, like Axel, does not provide any information beyond what is implicit in the '567 patent claims (i.e., expression of one exogenous DNA sequence encoding one immunoglobulin light chain polypeptide in one transformed host cell). See Harris Second Declaration, ¶ 66. Thus, Rice, like Axel, would not have suggested to or otherwise motivated a person of ordinary skill to modify the '567 patent claims to independently express exogenous DNA sequences encoding both an immunoglobulin light chain and an immunoglobulin heavy chain in a single transformed host cell followed by assembly of the expression products into a properly formed immunoglobulin molecule or fragment. See Harris Second Declaration, ¶ 67; Rice Second Declaration, ¶ 30.

Owners note that the Office cites the opinion of Dr. David Baltimore that "he and other working in the field would have expected that if two chains were expressed they would form a functional antibody" "without further testing of the idea" based on the "demonstration that an introduced light chain gene encoded a protein that would combine with an endogenous heavy chain ... ." The Office apparently relies on this third party opinion to support its view that a person of ordinary skill in the art would expect proper formation of immunoglobulin heavy and light chains once they are produced in a host cell.[29]

Initially, Owners note for the record that Dr. Baltimore is a Director of MedImmune, Inc., the real-party-in-interest of the third party that apparently requested ex parte reexamination of the '415 patent on December 23, 2005.[30] Dr. Baltimore did not indicate that he was affiliated with the third party requestor in his declaration, and the third party requestor itself fails to point this out in its request.

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[29] As explained above, it is improper for the Office to rely on third party opinions in an ex parte reexamination proceeding. The reexamination statute expressly limits the evidence that may be cited in requests for reexamination, as well as evidence used as the basis for substantial new questions of patentability identified by the Office, to "patents and printed publications." See In re Lonardo, 119 F.3d 960, 966, 43 U.S.P.Q.2d 1262 (Fed. Cir. 1997) (discussing kinds of evidence authorized for use in reexamination proceedings). Moreover, to the extent that the Office is permitted to review affidavits and declarations in the course of a reexamination proceeding, no rejection may be based on such affidavits and declarations. M.P.E.P. § 2258(I)(K).

[30] See Opening Brief of MedImmune, Inc. at 48, n. 18, MedImmune, Inc. v. Genentech, Inc., No. 05-608 (S.Ct. filed May 15, 2006).

By any measure, the personal views of Dr. Baltimore cannot be considered representative of the views of a person of ordinary skill in the art in early April of 1983. As Dr. Rice explains, Dr. Baltimore's perspectives are unique in the field, given his impressive background (e.g., Nobel Laureate in 1975, president of two prestigious academic research institutions, diverse knowledge across multiple scientific disciplines). See Rice Second Declaration at ¶¶ 7-10. See also Studiengeselleschaft Kohle mbH v. Dart Industries, 549 F.Supp. 716, 216 USPQ 381 (D. Del. 1982).[31]

Dr. Rice also explains that, contrary to Dr. Baltimore's contentions, a person of ordinary skill in the art in 1983 would not have made these types of assumptions about whether exogenous heavy and light immunoglobulin genes could be expressed in the specific cell line they used, much less whether they would result in functional immunoglobulin. See Rice Second Declaration at ¶¶ 20, 26, 30 and 57. Dr. Rice explains that this is due to the lack of understanding at the time of the molecular mechanisms controlling expression of immunoglobulin genes, and assembly of immunoglobulins. See Rice Second Declaration at ¶ 20.

Dr. Rice also notes that there are no observations in the Rice paper concerning potential use of their experimental system in the production of immunoglobulins tetramers using recombinant DNA techniques. See Rice Second Declaration at ¶¶ 32, 56. Instead, Dr. Rice notes that the conclusions and observations in the paper concern the cellular mechanisms that control immunoglobulin gene expression in B-cells, the focus of the work described in that paper. See Rice Second Declaration at ¶ 52. This observation is also consistent with Dr. Rice's recollection that Dr. Baltimore did not ever convey an opinion comparable to what he has included in his declaration to him while he was working in Dr. Baltimore's lab. See Rice Second Declaration at ¶ 54.

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[31] The district court in this case dismissed the perspectives of an expert having credentials very similar to those of Dr. Baltimore as not being representative of a person with an "ordinary" level of skill in the art. ("Zeigler's theorizing about the evolution in Fischer of ethyl aluminum compounds did not represent the application of "ordinary skill in the art of which said subject matter pertains. 35 U.S.C. §103. Zeigler was probably the world's leading authority on organo-aluminums. His '115 and '332 patents and the fact that he was awarded the Nobel Prize in 1963 further support the Court's findings in this respect."). Id.

In contrast to Dr. Baltimore's conclusory and unsupported opinions, the testimony of two scientists who were working in the field of the invention in early April of 1983 and who can describe the views of a person of ordinary skill in the art on Rice is entitled to substantial deference. Interconnect, 774 F.2d at 1138, 227 U.S.P.Q. at 547; see also In re Zeidler, 682 F.2d at 967, 215 U.S.P.Q. at 494 (C.C.P.A. 1982).

Thus, because Rice fails to provide anything beyond what the '567 patent claims implicitly require, the '415 patent claims cannot be portrayed as being obvious over the '567 patent claims in view of Rice. See Harris Second Declaration, ¶ 69; Rice Second Declaration, ¶ 40.

(iii) The Hypothetical Kaplan Disclosure Does Not Suggest Production of Multiple Immunoglobulin Chains in One Transformed Host Cell

The Office contends that "Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens" and that "using known molecular biology techniques, the mRNA's can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins." Second Office Action at page 23. The Office states that Kaplan further "teaches that a variety of host cells (e.g. bacteria and yeast) and plasmids (particularly pBR322) may be used to express recombinant heavy and light chains (see page 10, lines 1-33)." Id.

Kaplan is primarily directed to a method of making human hybridomas. There is a notional suggestion in Kaplan regarding construction of recombinant DNA molecules containing either an antibody heavy chain or an antibody light chain gene, expressing these genes in separate cells, and assembling the light and heavy chain proteins. Kaplan, however, provides no experimental results, examples or specific guidance regarding these methods of producing a heavy or light immunoglobulin chain polypeptide. See Harris Second Declaration, ¶ 69.

A person of ordinary skill in the art in early April of 1983 would not view the general proposals in Kaplan as suggesting or teaching that exogenous immunoglobulin heavy and light chain genes could or should be expressed in a single host cell. Neither would that person view the general proposals regarding single chain expression as predictive of success in transforming a

single host cell with exogenous immunoglobulin heavy and light chain DNA sequences. See Harris Second Declaration, ¶ 69.

As Dr. Harris explained previously, Kaplan does nothing more than illustrate a general hypothetical approach that one might explore in an attempt to express an individual heavy or light chain polypeptide in a transformed host cell. See Harris First Declaration, ¶¶40-41; see also Harris Second Declaration, ¶ 68. As Dr. Harris explains, a person of ordinary skill in the art in early April of 1983 would not have read Kaplan as suggesting or teaching that exogenous immunoglobulin heavy and light chain genes should be expressed in a single bacterial host cell. See Harris Second Declaration, ¶ 70.

Read properly, Kaplan adds nothing to what is already inherent to the '567 patent claims. Thus, Kaplan, like Axel and Rice, does not provide any suggestion or motivation to a person of ordinary skill in the art to modify the '567 patent claims as the Office asserts. See Harris Second Declaration, ¶70.

f. Dallas Would Not Have Provided Any Additional Motivation to a Person of Ordinary Skill in the Art in April of 1983 to Modify the '567 Claims in View of Axel, Rice or Kaplan

The Office cites Dallas, asserting that it would lead a person of ordinary skill in the art to modify the '567 claims when considered in view of view of Axel, Rice or Kaplan. Specifically, the Office asserts that Dallas teaches that "two different proteins (in addition to a selectable marker) can be expressed in a single cell" and that such expression can be accomplished by the use of one or two vectors (e.g., either one vector containing DNA encoding the two distinct proteins, or two vectors, each one containing one DNA encoding one protein). The Office then asserts that:

> the Axel, Rice and Kaplan references taken in view of the Dallas reference teaching would provide motivation to one of ordinary skill in the art at the time the instant invention was made to modify the Cabilly 1 patented invention to transform a single host with:
>
> a. the individual Cabilly 1 vectors separately containing a light or heavy chain; or

b. a modified Cabilly 1 vector encoding both an immunoglobulin light and heavy chain for independent expression of these chains.

Contrary to the assertions of the Office, Dallas would not have suggested to a person of ordinary skill in the art early April of 1983 what the Office asserts.

Dallas is directed to methods for expressing bacterial genes in E. coli cells, not production of eukaryotic proteins. See Harris Second Declaration, ¶ 72, Rice Second Declaration, ¶¶ 41-42. The significance of this distinction is explained by Dr. Harris at ¶ 72 of his Second Declaration, where he observes:

> A person of ordinary skill in the art in early April of 1983 would have understood that there were less significant challenges associated with expressing bacterial genes in an E. coli cell as compared to producing two large complex eukaryotic immunoglobulin proteins using recombinant DNA sequences alien to the E. coli cell.

Similarly, as Dr. Rice observes at ¶ 42 of his Second Declaration:

> I do not believe the *Dallas* reference would have resolved any of the questions and issues that I described concerning our 1982 *PNAS* paper. This is because the *Dallas* work concerns expression of bacterial genes in bacterial cells, not expression of eukaryotic genes in bacterial cells. The proteins that are produced by the *Dallas E. coli* cells are apparently not secreted by or recovered from the host cells. The bacterial genes in *Dallas* are much less complex than the eukaryotic immunoglobulin genes that are used in the '567 and '415 patent claims because, for example, bacterial genes do not contain introns. In addition, bacterial gene control elements and translational control elements were far better characterized and understood in early 1983 relative to eukaryotic systems.

Dallas also teaches that the purpose of transforming the E. coli cells with one or two exogenous bacterial genes is to create non-pathogenic E. coli cells for use as vaccines, not to produce desired polypeptides or proteins. See Harris Second Declaration, ¶ 76. As Dallas states, the objective of the invention "is to provide an improved vaccine employing toxoids or adhesins as to the antigenic determinants but which does not require purification and isolation of such substances." Dallas, page 3, lines 13-16 (emphasis added).

The limited technical complexity of the Dallas work, coupled with the questionable experimental results it reports, also would not have encouraged a person of ordinary skill to

broadly extend the teachings of Dallas. First, unlike the large (~150 kD for IgG), complex eukaryotic immunoglobulin tetramer protein, the bacterial protein antigens being produced in Dallas are small (about 30kD or less), simple, monomeric bacterial surface proteins. See Harris Second Declaration, ¶ 74. Second, in the examples showing more than one bacterial gene being expressed in a single E. coli cell, Dallas reports that lower levels of expression (relative to expression of the two proteins in separate, singly transformed cells) were observed, or that the transformed E. coli cells were not stable. See Harris Second Declaration, ¶ 77; Dallas at page 8. Dallas does not explain these results. See, Harris Second Declaration, ¶ 77. Thus, as Dr. Harris succinctly explains:

> I believe that one of ordinary skill in the art would have considered the cited portions of the Dallas publication to be a restatement of what was already well known at the time; namely, that one could introduce and express multiple bacterial genes (e.g., two different antibiotic resistance genes) using the same or different plasmids in a single bacterial host cell.

Harris Second Declaration, ¶ 73. To a person of ordinary skill in the art in early April of 1983, Dallas would not have provided insights concerning production of two eukaryotic proteins in a single transformed host cell. Dallas also does not explicitly or implicitly suggest that its findings or techniques can be extended to methods for producing multiple eukaryotic proteins in a single host cell. As such, a person of ordinary skill in the art in early April of 1983 would have considered Dallas to have almost no relevance to the subject matter of the '567 patent claims, whether considered alone or in view of Axel, Rice or Kaplan. See Harris Second Declaration, ¶ 78.

g. Deacon and Valle 1981 Do Not Remedy the Deficiencies of the Office's Rejection Based on the '567 Patent, Taken in View of Axel, Rice or Kaplan, Taken Further in View of Dallas

The Office cites Deacon and Valle 1981 for the proposition that these references "provide further motivation to perform the Cabilly 1 patented steps in a single cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering the production of a functional antibody with a reasonable expectation of success." Second Office Action, page 26. To support this assertion, the Office states that:

> Although the above-discussed Deacon and 1981 Valle reference utilize m-RNA, as compared to the use of vector DNA in the Cabilly 1 claims for

> encoding the corresponding light and heavy immunoglobulin chains, once the m-RNA or vector DNA is expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression. Accordingly, the difference between using vector DNA vs. mRNA for host transformation is not substantive.
>
> Accordingly, the Deacon [and] 1981 Valle . . . references taken separately or in combination provide further motivation to perform the Cabilly 1 patented steps in a single cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering obvious the production of a functional immunoglobulin with a reasonable expectation of success to one of ordinary skill in the art at the time the instant invention was made.

Second Office Action, pages 25-26 (emphasis added). The Office also asserts that:

> once the mRNA or vector DNA is expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression. Accordingly, the difference between using vector DNA vs. mRNA is not substantive.

Id., at page 26.

Thus, the Office asserts, first, that production of immunoglobulin tetramers via microinjection of Xenopus oocyte with mRNA fractions would have been viewed as a distinction without substance relative to transformation of host cells with DNA in early April of 1983, and, second, that experimental results reported in Deacon and Valle 1981 would establish to a person of ordinary skill in the art that it was reasonably likely that functional immunoglobulin would be formed in any type of host cell transformed with DNA sequences encoding immunoglobulin heavy chain and light chain polypeptides (i.e., that the formation of immunoglobulin tetramers would have been predictable based on the Xenopus experiments).

The Office mischaracterizes what is actually shown by the Deacon and Valle 1981 references, as well as the relevance this work would have to the '415 patent claims.

Initially, Owners invite the Office to consider the enclosed declaration under 37 C.F.R. § 1.132 of Dr. Alan Colman. Dr. Colman is a distinguished scientist and a recognized expert in the use of the Xenopus oocyte experimental translation system. Dr. Colman is also a co-author of the Valle 1981 and Valle 1982 publications and was the principal investigator of the work reported in those publications. Dr. Colman is familiar with the views of a person of ordinary

skill in the art in early April of 1983, and particularly, with what such a person would have been taught by the Deacon and Valle 1981 references. Owners also invite the Office to consider the opinions of Dr. Harris concerning these publications. See Harris Second Declaration, ¶¶ 87-97.

Owners reiterate that the views of qualified experts who can accurately describe the views a person of ordinary skill in the art would have had at the relevant period are highly probative of what a particular reference would or would not have taught.

The Deacon and Valle 1981 references describe results of experiments conducted in Xenopus oocytes. See Colman Declaration, ¶ 5. The experiments involve microinjection of a fraction of mRNA isolated from a lymphocyte that is actually producing immunoglobulin – indicating that the lymphocyte is successfully expressing its endogenous genes coding for the heavy and light immunoglobulin chains. See Harris Second Declaration, ¶ 95. The mRNA preparations isolated from such lymphocytes contain, in addition to mRNA transcripts produced incidental to the cell's transcription of the DNA sequences in its genes encoding the heavy and light immunoglobulin chains, mRNA transcripts corresponding to all the other genes that are being expressed by the cell. See Harris Second Declaration, ¶ 95. As described in Deacon and Valle 1981, the mRNA preparations are purified to varying degrees, and then physically injected into the cytoplasm of Xenopus oocytes.

It should be immediately appreciated by the Office that a Xenopus oocyte cannot, by any interpretation, be considered a "host cell" within the meaning of the '415 patent. See, e.g., discussion of host cells and attributes thereof provided at column 8, line 3 through column 10, line 29, of the '415 patent. As Dr. Colman explains:

> Initially, I believe a person of ordinary skill in early April of 1983 would have been familiar with the distinctions between an "oocyte" and a "host cell" as that term is used in the '415 and '567 patents. The large Xenopus oocyte, like other late stage oocytes, is primed to become an unfertilized egg cell given the right hormonal stimulation. Although after fertilization, the oocyte/egg becomes a "totipotent" one-cell embryo that can develop into any of the wide variety of differentiated cell types found in the mature frog, without fertilization it is incapable of dividing, and simply dies.
>
> According to the '415 patent, a host cell is a cell that has the capacity to be transformed with DNA sequences encoding the heavy and light chains of an immunoglobulin and to pass on to its progeny the genetic material that

> has been introduced into it. It and its progeny also have the ability to express the introduced DNA sequences. Because an oocyte cannot replicate, it cannot function as a host cell as I understand the meaning of that term from the '415 patent.

Colman Declaration, ¶¶ 18-19.

Moreover, a person of ordinary skill in the art in early April of 1983 would have been familiar with the various unique characteristics of the Xenopus oocyte relative to other types of cells, including oocytes from other species. See Colman Declaration, ¶¶ 15 and 18-23. Such unique features (e.g., enormous size, which permits unique physical manipulations; highly promiscuous translational capacity; extended viability) made the Xenopus oocyte a very useful experimental tool. However, it was recognized that these features also caused experimental results obtained in Xenopus oocytes to be viewed as not representative of what might be observed in differentiated cells, such as cells developed for use as host cells according to the '415 patent. As Dr. Colman explains at ¶ 24:

> . . . these properties of *Xenopus* oocytes were not considered by those working in this field as establishing that any given host cell would have the same properties when provided with any form of genetic information. Rather, the scientific community regarded the *Xenopus* oocyte system as an unusual, though highly useful, biological test bed. Consequently there was no suggestion at the time that the results observed in *Xenopus* oocytes could be extrapolated to other cell types.

See also Harris Second Declaration, ¶¶ 90-93 .

Both Dr. Colman and Dr. Harris each indicate that the results reported in Deacon and Valle 1981 involving mRNA-microinjected Xenopus oocytes would not have been considered by a person of ordinary skill in the art in early April of 1983 to be representative of what might occur in a host cell transformed with exogenous recombinant DNA encoding heavy and light immunoglobulin polypeptides. See Colman Declaration, ¶ 25; Harris Second Declaration, ¶ 97. As Dr. Colman explains in ¶ 15 of his declaration:

> . . . I do not believe a person of ordinary skill in the art, in early April of 1983, would have inferred from the demonstration of immunoglobulin assembly and secretion in *Xenopus* oocytes, that comparable results would have been expected to occur in mammalian cells, or, for that matter, in the other types of "host cells" that are described in the '415 patent (e.g., bacterial, yeast). As I explain below, persons of ordinary skill in the art

> would have considered the *Xenopus* oocyte to be an unusual cell. Also, the *Xenopus* work described in *Valle 1981* and *Deacon* does not answer significant questions that existed in early April of 1983 regarding assembly and secretion of immunoglobulins by mammalian cells. These questions involved issues such as how to control the timing of expression of the immunoglobulin genes, how to control the levels of such expression, the role of "molecular chaperone" proteins in the folding, assembly and secretion of the immunoglobulin, among other issues. Thus, I do not believe a person of ordinary skill in the art in early April of 1983, would have extrapolated the findings reported in the *Valle 1981* and *Deacon* papers concerning *Xenopus* oocytes to any type of host cell as has been suggested in the Second Office Action.

See also Harris Second Declaration, ¶ 93 ("As a result of the substantial differences between "host cells" and Xenopus oocytes that would have been known by a person of ordinary skill in the art in early April of 1983, I do not believe such a person would have considered the Xenopus oocyte model predictive of what would occur in a host cell transformed with recombinant DNA sequences, as required by the '415 patent claims.").

Thus, a person of ordinary skill in the art in early April of 1983 would not have extrapolated the experimental results in Xenopus oocytes, as reported in Deacon and Valle 1981, to genetically transformed host cells.

Drs. Colman and Harris also dispute the Office's assertion that the injection of mRNA fractions into Xenopus oocytes presents no substantive distinctions relative to transformation of host cells with exogenous DNA sequences that would affect the expectations of a person of ordinary skill as to whether the cells would produce immunoglobulin tetramers. For example, Dr. Colman explains that there are numerous distinctions of substance between the two systems that would fundamentally call into question the premise of the Office. As he states at ¶ 15 of his Declaration:

> [T]he work in *Xenopus* oocytes bypasses the significant questions that existed in early April of 1983 regarding the relationship between transcription of exogenous immunoglobulin genes and the subsequent production of intact immunoglobulins. This is because the oocyte experiments employ messenger RNA (mRNA) which has been extracted from cells specialized for, and which actually are producing, functional immunoglobulin. Thus, contrary to the views expressed in the Second Office Action, I believe a person of ordinary skill in the art, in early April of 1983, would have considered the distinctions between producing

> immunoglobulins in host cells using DNA and the translation of mRNA fractions encoding heavy and light immunoglobulin chain polypeptides in *Xenopus* oocytes to have been quite significant.

Dr. Harris also disagrees with the Office's view that a person of ordinary skill in the art would consider there to be no substantive distinctions between the DNA-based '415 process and the mRNA-based Xenopus oocyte experiments described in Deacon and Valle 1981. For example, Dr. Harris explains that "mRNA is itself the product of the expression of genes or an introduced DNA sequence by the transcriptional processes of the cell." See Harris Second Declaration, ¶ 95. Dr. Harris also provides examples of substantive distinctions "that would lead them to question whether the results seen in the *Xenopus* oocytes microinjection experiments would be observed in transformed host cell systems required by the '415 patent claims." See Harris Second Declaration, ¶ 96; see also, Colman Declaration, ¶¶ 26-35. Dr. Harris concludes (at ¶ 97) that:

> Accordingly, I do not agree that a person of ordinary skill would have considered the differences between using mRNA fractions in *Xenopus* experiments and the processes of transforming host cells with recombinant DNA sequences specified in the '415 patent claims to be non-substantive. I also do not agree that the *Xenopus* experiments made predictable or otherwise taught a person of ordinary skill how to achieve in a host cell the results observed in these oocyte experiments, because these experiments do not address the significant challenge of producing a transformed host cell that functions as required by the '415 patent claims (*i.e.*, by inserting recombinant DNA sequences encoding heavy and light chain polypeptides and obtaining the successful transcription and translation of those DNA sequences).

Owners submit that the Office has incorrectly interpreted the significance and relevance of Deacon and Valle 1981. In particular, the Office improperly dismisses the significant distinctions that a person of ordinary skill in the art would have immediately appreciated as existing between transcription in transformed host cells of exogenous DNA sequences encoding heavy and light immunoglobulin chains, and translation in a Xenopus oocyte of injected mRNA fractions obtained from a lymphocyte that has successfully expressed its endogenous immunoglobulin genes. See Colman Declaration, ¶¶ 35-36. As Dr. Colman explains, a person of ordinary skill in the art would have viewed the latter experiment to be a very significant shortcut that could not be taken in the case of stably transformed host cells. See Colman Declaration, ¶¶ 15, 30.

Because the Deacon and Valle 1981 experiments would be viewed as being substantively different from immunoglobulin production via transformed host cells, and because neither Deacon nor Valle 1981 would have provided insights relevant to production of immunoglobulin tetramers in host cells transformed with exogenous DNA sequences encoding the light and heavy immunoglobulin chains as the Office asserts, Owners respectfully submit these publications would not have provided any further motivation to the person of ordinary skill in the art to modify the '567 claims in view of Axel, Rice, or Kaplan, taken further in view of Dallas. See Harris Second Declaration, ¶97.

h. Ochi Does Not Remedy the Deficiencies of the Office's Rejection Based on the '567 Patent, Taken in View of Axel, Rice or Kaplan, Taken Further in View of Dallas

The Office cites Ochi as an alternative basis for its proposition that one would have been provided "further motivation to modify the Cabilly 1 patented steps in a single cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering obvious the production of a functional immunoglobulin with a reasonable expectation of success to one of ordinary skill in the art at the time the instant invention was made." See Second Office Action at page 26. For reasons comparable to those set forth above, Ochi does not remedy the deficiencies of the Office's rejection of the claims of the '415 patent over the claims of the '567 patent, considered alone, or in view of Axel, Rice, Kaplan, or further in view of Dallas.

Ochi describes an experiment in which a light chain gene encoding an anti-TNP immunoglobulin light chain polypeptide was isolated from a hybridoma, and was subsequently used to transfect a mutant cell line derived from that hybridoma. See Harris Second Declaration, ¶ 80; Rice Second Declaration, ¶ 34. The mutant line did not express the anti-TNP light chain gene but did express its endogenous anti-TNP heavy chain gene along with the heavy and light chain genes contributed to the hybridoma from the fusion partner. See id. Ochi did not attempt to transfect cells with a heavy chain gene, or with both heavy and light chain genes. See Second Harris Declaration, ¶ 82-84. Ochi observed that functional immunoglobulin was produced by the mutant light-chain transformed hybridoma line. See Second Harris Declaration, ¶ 84.

The Office asserts that this demonstration would have led a person of ordinary skill in the art to "reasonably expect" production of functional immunoglobulin in situations where a host

cell (of any type) is transformed with DNA sequences encoding heavy and light chains. Owners respectfully disagree.

Ochi, similar to Rice, describes an experiment where only one exogenous light chain gene was used to transfect a hybridoma cell line that was already expressing its endogenous heavy chain genes and at least one light chain gene. See Harris Second Declaration, ¶¶ 80-81; Rice Second Declaration, ¶ 34-35. The Ochi work, as Dr. Harris explains, was designed to ensure that there would be success. As he explains (at ¶¶ 83-84):

> The authors of the Ochi paper also did not suggest that their transfection and expression results would be broadly extendable to any type of cell line or situation. Instead, they chose to employ very limited experimental conditions to test a basic hypothesis — whether one could restore gene expression in a cell line that, due to a random mutation, lost its ability to express the same gene. They describe the limited nature of their experimental design in their abstract at page 340, where they state:
>
> > The mechanisms responsible for the regulation of the expression of rearranged immunoglobulin genes is poorly understood. The technique of modifying cloned genes *in vitro* and transferring the modified genes to cells in culture provides a tool for identifying the structural features required for gene expression. ... To analyse immunoglobulin genes in this manner, however, it is first necessary to use, as recipients, cells that normally permit immunoglobulin production. (Emphasis added.)
>
> I believe a person of ordinary skill in the art would not broadly extend the observations and findings in the Ochi paper as the Office suggests; namely, to reasonably expect that one could transform a single B-cell with recombinant DNA sequences encoding light and heavy chain polypeptides, achieve successful expression of the introduced genes, and achieve assembly of functional immunoglobulin tetramers.

Despite the relatively limited nature of this experiment – restoration of a lost expression of a light chain gene expressed by the parent of the cell line used – the Ochi authors do not portray their results as being reasonably predictable or widely extendable, as the Office suggests. Rather, the Ochi authors acknowledge that they were unable to explain how the transformed hybridoma cells were able to produce the results they observed. See Harris Second Declaration, ¶ 85; Rice Second Declaration, ¶ 36. Moreover, the experimental design of the work described in Ochi – insertion of an anti-TNP light chain gene into a cell whose parental line had expressed

that gene, and which was continuing expression of its heavy chain genes and its remaining light chain gene – limits the expectations that one of ordinary skill would have had as to whether the Ochi experimental procedures could be extended more generally. See Harris Second Declaration, ¶ 83 (pointing out that Ochi observed that it was "necessary to use, as recipients, cells that normally permit immunoglobulin production").

Dr. Rice, a person with relevant experience in the field of the Ochi experiments, has similar views regarding the significance of the Ochi results. As he explains at ¶ 37 of his second declaration:

> Even though the experimental design of the *Ochi* work seems relatively straightforward in hindsight (*i.e.*, restoring lost expression of a light chain gene), their results were considered significant enough to be published in Nature, which at the time was, and still is, considered to be one of the most prestigious peer-reviewed scientific journals in the world. This shows how non-routine expression of even a single exogenous immunoglobulin gene was in early April of 1983.

The inferences being drawn by the Office as to reasonable expectations based on the Ochi results associated with transfection and expression of an exogenous light chain gene, plainly, are not warranted.

Thus, Ochi would not have been read by a person of ordinary skill in the art in early April of 1983 as the Office suggests. See Rice Second Declaration, ¶¶ 33, 44; Harris Second Declaration, ¶ 86. Ochi, like Axel, Rice and Kaplan, does not provide any information beyond what is implicit in the '567 patent claims (i.e., expression of one exogenous DNA sequence encoding one immunoglobulin light chain polypeptide in one transformed host cell). See Harris Second Declaration, ¶ 86. Accordingly, Owners submit that Ochi does not remedy the shortcomings of the rejection of the '415 claims based on the '567 claims taken in view of Axel, Rice or Kaplan, taken further in view of Dallas.

D. The Dependent Claims of the '415 Patent Are Not Obvious

1. The Rationale for the Rejections of the Dependent Claims is Fundamentally Improper

Owners note first that, for the reasons discussed above, the Office has not set forth a prima facie showing that any of the independent claims are obvious over the claims of the '567

patent, either taken alone or in view of any or all of Axel, Rice, Kaplan, Dallas, Deacon, Valle 1981 or Ochi. Accordingly, dependent claims 5-10, 12, 14, 19-20, 22, 26-32 and 34-36 are patentable because the claims from which they depend are patentable. In re Fine, 837 F.2d 1071, 1076, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious."(citations omitted)).

The rejection of dependent claims 5-10, 12, 14, 19, 20, 22, 26-32, and 34-36 is premised on the assertion that the '567 patent claims "encompass" ("read on") methods requiring the limitations of the dependent claims of the '415 patent. The Office advances these rejections notwithstanding the fact that it acknowledges that the claims of the '567 patent do not recite or require the limitations in question. As discussed above, it is simply improper to read limitations into the claims of the '567 patent that are not there. Furthermore, the claims of the '567 patent do not and cannot be cited by the Office as providing any "suggestion" for modifying themselves in a way that would result in any of the claims of the '415 patent. See General Foods Corp., 972 F.2d at 1281, 23 USPQ2d at 1846. Moreover, the '415 patent specification cannot be cited as evidence suggesting any modification of the '567 patent claims. See In re Vogel, 422 F.3d at 441, 164 USPQ at 621-22.

For the additional reasons stated below, the cited subsidiary references do not render the dependent claims obvious, and they do not address the deficiencies of the grounds of rejection stated with respect to the independent claims.

2. The Cited Subsidiary References Provide No Evidence or Guidance That Makes the Dependent Claims Obvious

The Office cites various publications for disclosures it believes are relevant to certain dependent claim limitations. The discussion below follows the order in which the claims are treated at pages 26-32 of the Office Action.

a. Claim 5

The Office notes that the claims of the '567 patent do not require the use of a pBR322 vector. The Office cites Axel and Kaplan for the teaching that pBR322 is a plasmid that is useful for expressing heterologous proteins. Based on this teaching, the Office concludes that the invention of instant claim 5 is obvious. Neither of these references teaches that pBR322 is

particularly suitable for expressing DNA sequences encoding immunoglobulin heavy and light chain polypeptides in a single transformed host cell. Accordingly, these references, alone or together, do not provide motivation to modify the base claims to arrive at the invention as claimed in claim 5.

b. Claims 6-8, 19, 20, and 26

The Office states that claims 6-8, 19, 20, and 26 differ from the claims of the '567 patent in "using bacterial/yeast/mammalian host cells including E. coli strain X1776." The Office thus agrees that none of the claims of the '567 patent requires any of these host cell types.

Axel and Rice are cited for teaching the use of mammalian host cells. Neither of these references teaches that any particular cell type would be suitable for co-expressing immunoglobulins in transformed host cells. Notwithstanding the fact that the basic marker gene technology described in the Axel reference ultimately proved to be a useful tool for realizing various processes, including processes used in the present invention, Axel simply does not speak to any co-expression strategy. See Second Harris Declaration, ¶¶ 35-48. Rice describes only a single host cell – the 81A-2 cell line. For the reasons discussed at length above and in the First and Second Declarations of Dr. Rice, this cell line is unsuitable for co-expressing introduced heavy chain and light chain polypeptides because it is continuously expressing an endogenous heavy chain gene. See Rice First Declaration, ¶¶ 7, 11-12; Rice Second Declaration, ¶ 18. Thus, Rice does not describe or suggest any cell line that would be suitable for the practice of the invention claimed in instant claims 6-8, 19, 20, and 26.

Kaplan is said to teach that bacteria and yeast cells can be used as host cells for producing immunoglobulin chains. However, Kaplan does not teach or suggest that any host cell should be used for co-expressing heavy chain and light chain genes, as Dr. Harris explains in his Second Declaration at ¶¶ 68-70. Nothing in Kaplan would reasonably lead one of ordinary skill to expect that these microbial host cells would be useful in a co-expression process.

Finally, none of Axel, Kaplan, or Rice even identifies E. coli X1776, let alone teaches why it would be useful for any particular purpose. The Office has identified no evidence in the prior art that is even marginally relevant to the use of this particular host cell type according to the claimed invention.

Because the cited references do not supply any reason, motivation, or expectation of success for using various host cell types according to the methods of claims 6-8, 19, 20, and 26, they do not support a prima facie case of unpatentability.

c. Claims 9 and 29

The Office recognizes that claims 9 and 29 differ from the claims of the '567 patent in that they require the secretion of a functional antibody protein from a host cell, a feature which is not recited or required by the '567 patent claims. In an attempt to bridge this gap, the Office relies on the generic disclosure of mammalian host cells in Axel and on the description of cells that express introduced light chain polypeptides in Rice. Neither reference, however, states or suggests anything about the secretion of functional antibodies by mammalian host cells transformed with DNA encoding heavy chain and DNA encoding light chain immunoglobulin polypeptides.

Axel, as noted above, merely describes certain mammalian host cells that are suitable for use in conjunction with its basic marker gene technology. Also, because Axel does not address expression of two polypeptides of interest – such as an immunoglobulin heavy and an immunoglobulin light chain polypeptide – it similarly does not address production and secretion of a functional immunoglobulin molecule or fragment.

As Dr. Rice explains in his First Declaration, the experiments described in Rice are not capable of producing any functional antigen-binding antibody molecules because the endogenous heavy chain does not have the same antigen binding specificity of the exogenous light chain gene used to transfect the cell line. See Rice First Declaration, ¶¶ 11, 16. Moreover, Rice does not contain any disclosure regarding whether the 81A-2 cell line secretes, or is capable of secreting, any immunoglobulin tetramer. See Rice Second Declaration, ¶ 17. Thus, Rice contains no teaching or suggestion that would lead one of ordinary skill to prepare any type of host cell, transformed or otherwise, with the expectation that it would be useful for preparing secreted, functional antibody tetramers.

As neither Axel nor Rice specifically suggests production of an immunoglobulin molecule or a functional fragment via secretion by a transformed host cell, these references do not support a prima facie case of unpatentability as to claims 9 and 29.

d. Claims 10 and 27-32

The Office states that claims 10 and 27-32 require further limitations involving expression of insoluble immunoglobulin polypeptides, solubilization of such polypeptides, and refolding of the solubilized polypeptides to produce functional antibody molecules. The Office acknowledges that the claims of the '567 patent do not require limitations that correspond to the limitations of claims 10 and 27-32 of the '415 patent.

Kaplan and Builder are cited as being relevant to expression and solubilization of immunoglobulin polypeptides in host cells such as E. coli. Kaplan does not teach or suggest that any host cell should be transformed with first and second DNA sequences encoding immunoglobulin heavy and light chains, and it does not address solubilizing and refolding a heterogeneous mixture of different immunoglobulin polypeptides. Builder provides disclosure that is relevant to the generic problem of refolding recombinant polypeptides, but it contains no specific suggestion regarding refolding compositions containing constituent polypeptides of a multimeric protein that have been independently produced in a cell, such as is required by the claims of the '415 patent.

Dr. Harris explains the structural complexity of an immunoglobulin tetramer. See Harris Second Declaration, ¶¶ 13 to 18. Particularly in view of his observations, the generic disclosure in the cited references cannot be said to provide any specific direction that make claims 10 and 27-32 prima facie obvious in view of the claims of the '567 patent. Thus, neither Kaplan nor Builder, alone or together with any other references of record, suggests modifying the '567 claims so as to yield claims 10 and 27-32.

e. Claim 12

The Office notes that claim 12 of the '415 patent differs from the claims of the '567 patent as it requires the use of constant and variable domain DNA sequences from the same source antibody DNA. Not only is this feature not recited in the claims of the '567 patent, it is specifically excluded from the claims of that patent because they require the production of chimeric antibody chains. Moreover, the Office cites no prior art evidence that indicates why a method of making a tetrameric immunoglobulin molecule comprising a coding sequence having

DNA from a single source would be an obvious modification of a method of making a single immunoglobulin polypeptide that is required to use DNA from different sources.

Because the Office has cited no evidence that addresses the further limitation of claim 12, it has not set forth a prima facie case of unpatentability as to that claim.

f. Claim 14

Claim 14 requires the use of immunoglobulin DNA from a hybridoma source, a feature that, as the Office observes, is not recited or required by any claims of the '567 patent. The Office notes that Kaplan teaches that hybridomas are sources of mRNA encoding antibody chains for recombinant expression. However, as discussed at length above, Kaplan does not teach or suggest recombinant expression of immunoglobulin heavy chain and light chain polypeptides in a single host cell. Thus, Kaplan does not provide evidence that supports the obviousness of the invention of claim 14 as a whole.

g. Claim 22

Claim 22 requires the production of the immunoglobulin heavy chain and light chain polypeptides of an anti-CEA antibody, a feature which is not recited in any of the claims of the '567 patent. The Office notes that Accolla describes anti-CEA monoclonal antibodies. Such disclosure, however, does not address the obviousness of the invention of claim 22 as a whole. Because Accolla does not teach or suggest producing antibodies directed against CEA or any other antigen in a transformed host cell system, that reference does not support a prima facie case of unpatentability. Claim 22 is separately patentable over the claims of the '567 patent.

h. Claims 34-36

Finally, the Office discusses claims 34-36, which depend from various claims and require the further step of attaching the antibody or antibody fragment to a label or drug. This step is neither implicit nor required by any claim of the '567 patent. The Office cites Kaplan for generic disclosure relating to the use of drug-conjugated or radiolabeled antibodies for therapy or diagnosis. This generic disclosure, however, adds nothing to the deficient rationale advanced by the Office concerning the use of a transformed host cell for production of an immunoglobulin molecule. Thus, because Kaplan does not provide evidence that establishes that the inventions as

a whole of claims 34-36 are obvious in view of the claims of the '567 patent, the Office's conclusion that these claims are obvious is improper.

III. Conclusion

In view of these remarks, Owners respectfully submit that claims 1-36 of the '415 patent are not unpatentable for reasons of obviousness-type double patenting over any of the claims of the '567 patent, taken in view of Axel, Rice or Kaplan, taken further in view of Dallas, taken further in view of Deacon, Valle 1981 or Ochi, and taken further in view of Builder or Accolla. Owners respectfully submit that all issues raised by the Office and outstanding from the Second Office Action have been fully addressed, and that no grounds exist for refusing to grant Owners a reexamination certificate affirming the patentability of claims 1-36 of the '415 patent.

Pursuant to the interview of September 27, 2006, Owners respectfully request that the Examiner with primary responsibility for this merged reexamination proceeding contact the undersigned if any matter believed to be raised by the Second Office Action has not been fully addressed by this response.

The Commissioner is hereby authorized to charge Deposit Account No. 18-1260 for any additional fees required in connection with the filing of this Response.

Respectfully submitted,

Date: October 30, 2006

By: _____
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EXHIBIT A

Illustrative Differences between '567 and '415 Patent Claims

'567 patent claim 1	'415 patent claim 1
1. A method comprising:	1. A process …
	for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains comprising the steps of:
(a) preparing a DNA sequence encoding a chimeric* immunoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species; (b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell; (c) transforming the host cell with the vector of (b); (d) culturing the host cell; and	(i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain
(e) recovering the chimeric heavy or light chain from the host cell culture	
	(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.

* As recognized by the Office, '415 patent claim 1 does not require that the chain (or fragment) be chimeric.